IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

THE UNITED STATES OF AMERICA, Plaintiff, v. GILEAD SCIENCES, INC. AND GILEAD SCIENCES IRELAND UC, Defendants.	C.A. NO.: **JURY TRIAL DEMANDED**

COMPLAINT

1. The human immunodeficiency virus (HIV) is the cause of the acquired immunodeficiency syndrome (AIDS) epidemic. Since the beginning of the AIDS epidemic in the early 1980s, researchers worldwide have sought vaccines or other biomedical strategies to effectively prevent the spread of HIV. For over two decades, none succeeded. During that time, over 25 million people died due to AIDS. And the number of people living with HIV reached its highest level—about 40.3 million people.

2. Then in the mid-2000s, researchers at the Centers for Disease Control and Prevention (CDC) succeeded where others had not. Using new and precise animal modeling methods, these scientists conceived of and developed innovative two-drug regimens that could, for the first time, effectively prevent new HIV infections. These regimens consist of (1) emtricitabine (FTC) and (2) tenofovir or a tenofovir prodrug. This type of regimen is known as pre-exposure prophylaxis or PrEP.

3. CDC's unexpectedly effective regimens were even more remarkable because they came about at a time when many in the scientific community questioned whether any PrEP

regimen could safely and effectively prevent the spread of HIV. Even after CDC publicly shared its results, skepticism remained.

4. As a result of CDC's breakthrough, two human PrEP trials already underway changed their drug regimens to match CDC's new PrEP regimens. These studies, and others, confirmed that, when used as directed, CDC's PrEP regimens are 99 percent effective in preventing new HIV infections. Hundreds of millions of taxpayer dollars funded much of that clinical work.

5. The United States Patent and Trademark Office (PTO) granted CDC four patents that protect its innovative regimens and the taxpayers' investment. These patents entitle CDC to license its PrEP regimens and receive a reasonable royalty for their use.

6. Gilead Sciences, Inc., and Gilead Sciences Ireland UC manufacture, market, and sell Truvada® and Descovy®. Each of these products includes a combination of (1) FTC and (2) a tenofovir prodrug. When administered as a PrEP regimen, both are effective two-drug regimens claimed and protected by CDC's patents. Originally, Gilead had obtained FDA approvals for those products to be used for treating HIV in combination with other drugs. But after CDC's groundbreaking PrEP work and subsequent human trials, Gilead also obtained FDA approvals for Truvada®, and more recently Descovy®, to be used as PrEP regimens.

7. Gilead now markets and sells Truvada® and Descovy® as PrEP regimens that are protected by CDC's patents. And PrEP sales are one of the primary drivers for the growth of Gilead's HIV products.

8. As its PrEP sales have skyrocketed, Gilead has exaggerated its role in developing PrEP. In so doing, Gilead has ignored CDC's clear contributions and baselessly denied the validity

of CDC's patents. Gilead's only contribution to CDC's patented research was providing samples of the drugs that CDC used for testing purposes.

9. Gilead has repeatedly refused to obtain a license from CDC to use the patented regimens. Meanwhile, Gilead has profited from research funded by hundreds of millions of taxpayer dollars. Indeed, Gilead has reaped billions from PrEP through the sale of Truvada® and Descovy®, but has not paid any royalties to CDC. Accordingly, Gilead has willfully and deliberately induced infringement of CDC's patents and continues to do so. These actions by Gilead give rise to the present suit.

I. NATURE OF THE ACTION

10. The United States of America brings this civil action for patent infringement under 35 U.S.C. § 271 *et seq.* against Gilead Sciences, Inc. and Gilead Sciences Ireland UC (collectively, Gilead) for infringement of U.S. Patent Nos. 9,044,509 (the '509 Patent), 9,579,333 (the '333 Patent), 9,937,191 (the '191 Patent) and 10,335,423 (the '423 Patent) (collectively, the Patents-in-Suit) (Exhibits 1–4, respectively).

II. PARTIES

11. Plaintiff is the government of the United States of America (United States or Government) acting on behalf of its Department of Health and Human Services (HHS), headquartered at 200 Independence Avenue, S.W., Washington, D.C. 20201.

12. HHS is the owner of the Patents-in-Suit as set forth herein, by virtue of its administrative control of CDC, which is headquartered at 1600 Clifton Road NE, Atlanta, Georgia 30329.

13. Defendant Gilead Sciences, Inc. is a Delaware corporation, with a principal place of business at 333 Lakeside Drive, Foster City, California 94404.

14. Defendant Gilead Sciences Ireland UC (formerly known as Gilead Sciences Limited) is an unlimited liability company formed under the laws of Ireland, with a principal place of business at IDA Business & Technology Park, Carrigtohill, County Cork, Ireland. Gilead Sciences Ireland UC is a wholly owned subsidiary of Gilead Sciences, Inc. On information and belief, Gilead Sciences Ireland UC manufactures, packages, and labels Truvada® and Descovy® products that are marketed, distributed, and sold for PrEP in the United States.

15. On information and belief, Gilead Sciences, Inc., and Gilead Sciences Ireland UC (collectively, Gilead) work in concert to manufacture, import, market, distribute, label, and sell Truvada® and Descovy® for PrEP in this judicial District and throughout the United States.

III. JURISDICTION AND VENUE

16. This Court has subject matter jurisdiction over this action, pursuant to 28 U.S.C. §§ 1331 and 1338(a).

17. This Court has personal jurisdiction over Gilead Sciences, Inc., because it is a Delaware corporation and has purposefully availed itself of the rights and benefits of Delaware law. In particular, it recently commenced litigations in this District asserting patents relating to Truvada® and methods of using it to treat HIV-positive children. *See, e.g.*, *Gilead Sciences, Inc. et al. v. Aurobindo Pharma Ltd. et al.*, No. 1-18-cv-00765, filed May 18, 2018 (asserting patents relating to the active ingredients in Truvada® and methods for treating HIV infection in children with the active ingredients in Truvada®); *Gilead Sciences, Inc. et al. v. Amneal Pharms. LLC*, No. 1-17-cv-00943, filed Jul. 13, 2017 (same). Furthermore, on information and belief, Gilead Sciences, Inc. has engaged in substantial and continuing contacts with Delaware, including directing sales of or offers for sale of Truvada for PrEP® and Descovy® for PrEP in this District.

18. This Court has personal jurisdiction over Gilead Sciences Ireland UC. On information and belief, at the direction of Gilead Sciences, Inc., Gilead Sciences Ireland UC has

engaged in substantial and continuing contacts with Delaware. In particular, Gilead Sciences Ireland UC has manufactured Truvada for PrEP® and Descovy® for PrEP, products that are labeled, marketed, distributed, and sold to residents of Delaware. Furthermore, this Court also has personal jurisdiction over Gilead Sciences Ireland UC because it has purposefully availed itself of the rights and benefits of Delaware law as a plaintiff in other patent cases in this District. *See, e.g.*, *Janssen Pharmaceutica, N.V. et al. v. Mylan Pharms., Inc.*, No. 1-15-cv-00760, filed Aug. 31, 2015; *Gilead Sciences, Inc. et al. v. AbbVie, Inc.*, No. 1-15-cv-00399, filed May 19, 2015.

19. On information and belief, Gilead Sciences, Inc. and Gilead Sciences Ireland UC work in concert to regularly and continuously transact business within the State of Delaware, by selling pharmaceutical products in Delaware, including Truvada® and Descovy®, either on their own or through their affiliates.

20. On information and belief, Gilead derives substantial revenue from selling Truvada for PrEP® and Descovy® for PrEP throughout the United States, including in Delaware.

21. Venue is proper in this Court pursuant to 28 U.S.C. §§ 1391 and 1400(b) because Gilead Sciences, Inc. resides in this District. And pursuant to 35 U.S.C. § 1391(c)(3), venue is proper in this District for Gilead Sciences Ireland UC.

IV. TECHNICAL AND HISTORICAL BACKGROUND

A. The Human Immunodeficiency Virus

22. HIV is the virus responsible for the disease known as acquired immunodeficiency syndrome or AIDS.

23. HIV is a retrovirus, a type of virus that contains ribonucleic acid (RNA) as its genetic material. Retroviruses have an enzyme—reverse transcriptase—which allows the virus to transcribe its RNA into deoxyribonucleic acid (DNA) after entering a cell. To replicate, a retrovirus like HIV inserts a DNA copy of its genome into a host cell.

24. There, the DNA copy of the viral genome (proviral DNA) can serve as a template for the production of HIV in the host cell. In this manner, HIV targets, infects, and ultimately destroys cells associated with the human immune system, most notably a type of white blood cell called $CD4^+$ (or helper) T cells.

25. The loss of $CD4^+$ T cells due to an HIV infection, if untreated, ultimately leads to AIDS. Specifically, as the infection progresses, HIV begins to infect the $CD4^+$ T cells more efficiently. Although the body tries to make new T cells, the immune system is ultimately overwhelmed, leading to an extreme lowering of the $CD4^+$ T cell levels, and in turn, an immunodeficiency. Additionally, the high levels of HIV replication lead to a state of global immune activation that adds further to the inability of the immune system to function effectively.

26. The extremely low levels of $CD4^+$ T cells during AIDS makes a person vulnerable to a number of opportunistic infections and cancers that would generally not occur in persons with normally functioning immune responses. These opportunistic infections and cancers are frequently the direct cause of the death of a person with AIDS.

27. There are two major types of HIV: HIV-1 and HIV-2. Though both viruses can affect the human body similarly, weakening a person's immune system and leaving them more vulnerable to other infections and disease, they are genetically distinct and the course of disease and the recommended antiretroviral treatments may be different. Most HIV research is focused on HIV-1, as it is the type predominantly seen worldwide, and is the leading cause of HIV-associated morbidity and mortality.

28. Even with early intervention and effective treatment, many people living with HIV endure a persistent activation of the immune system, raising their risk for a number of diseases, including heart attack, vascular disease, and stroke.

29. Left untreated, almost all people living with HIV develop AIDS and eventually die of opportunistic infections and cancers.

B. The HIV/AIDS Epidemic

30. According to The Joint United Nations Programme on HIV and AIDS (UNAIDS), through 2018, 74.9 million people worldwide have been infected with HIV. Since the start of the epidemic in the early 1980s, 32 million people have died from AIDS-related illnesses, with 770,000 people dying in 2018 alone. Of the more than 37 million people currently living with HIV, UNAIDS reports that approximately 23 million people are receiving antiretroviral therapy (ART) to treat HIV.

31. Improved access to ART regimens that durably suppress the virus prevents the development of AIDS in persons living with HIV and decreases the likelihood of transmission of HIV to other people. Rates of HIV infection and new AIDS cases have decreased significantly because of this better treatment of HIV-positive persons as well as improved prevention efforts.

32. Since 2000, according to UNAIDS and World Health Organization (WHO) global estimates, annual diagnoses of new HIV infections have fallen by 37 percent, and deaths from AIDS-related illnesses have fallen by 45 percent. Even so, approximately 1.7 million people globally were infected with HIV in 2018.

33. In the United States, CDC reports that since the beginning of the epidemic over 675,000 people have died from AIDS-related illnesses. And roughly 38,000 Americans are newly infected with HIV each year. Of the more than 1.1 million people living with HIV in the United States, approximately 14 percent (1 in 7) are unaware that they are infected.

34. Efforts to end the epidemic, in the United States and worldwide, continue today.

C. Treatment of HIV Infections

35. Current HIV treatments are highly effective, but not curative. Available treatments help people with HIV live longer, healthier lives, but do not eliminate the virus from the human body or prevent reemergence of the virus when treatment is discontinued.

36. An HIV infection has been historically difficult to treat, in part, because of the virus' ability to mutate in response to antiretroviral drugs and drug regimens. This generally leads to drug-resistant strains of HIV.

37. Since approval of the first anti-HIV (antiretroviral) drugs in the 1980s, treatment strategies have evolved to use a combination of drugs (from different classes of drugs) to durably suppress HIV replication below levels in the blood that can be detected by currently licensed assays. Today, ART involves administration of a combination of multiple drugs or "combination therapy." HIV-positive patients taking ART are administered a daily combination of antiretroviral medicines, and these regimens generally include three antiretroviral medicines from at least two different drug classes. In this manner, ART acts against HIV replication to consistently keep a patient's viral load (a measure of the amount of virus in the bloodstream) below detectable levels.

38. There are several classes of antiretroviral drugs used to treat HIV infections effectively, including (i) nucleoside reverse transcriptase inhibitors (NRTIs) and nucleotide reverse transcriptase inhibitors (NtRTIs), (ii) nonnucleoside reverse transcriptase inhibitors (NNRTIs), (iii) protease inhibitors (PIs), (iv) integrase inhibitors, and (v) entry or fusion inhibitors.

39. NRTIs and NtRTIs function as analogs of the naturally occurring deoxynucleosides and deoxynucleotides needed to synthesize the viral DNA. Thus, they can disrupt the reverse transcription process needed to generate the HIV DNA, thereby preventing integration of the proviral DNA into the genome of human cells.

40. Treatment with NRTIs and NtRTIs over extended periods of time can result in toxicity. Drug-related toxicity may include a variety of outcomes, including anemia, loss of kidney function, and decreased bone density. And the toxicity may vary by regimen.

41. While new NRTIs and NtRTIs are increasingly less toxic, toxicity concerns existed during the development of the Patents-in-Suit and remain today. These concerns are heightened when two drugs of these types are co-administered to healthy persons on a daily basis.

42. Presently, a typical ART regimen consists of a "backbone" of two NRTI/NtRTIs in combination with either an integrase inhibitor, an NNRTI, or a PI.

43. By 2005, the relevant HHS HIV-treatment guidelines included seven different NRTI/NtRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zidovudine), one NNRTI (efavirenz), six PIs (atazanavir, fosamprenavir, indinavir, nelfinavir, ritonavir, and saquinavir), and one fusion inhibitor (enfuvirtide), as well as five fixed-dose combination tablets of certain drugs listed above, for use as part of an ART regimen with previously untreated (treatment naïve) patients.[1]

44. The current HHS guidelines' Recommended Antiretroviral Regimens for Initial Therapy set forth five different NRTI/NtRTIs (abacavir (ABC), emtricitabine (FTC), lamivudine (3TC), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF)), three NNRTIs (doravirine (DOR), efavirenz (EFV), and rilpivirine (RPV)), four integrase inhibitors (bictegravir

[1] *See* Panel on Clinical Practices for Treatment of HIV Infection Convened by the Department of Health and Human Services, *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*, 8–15 (Apr. 7, 2005), https://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL04072005001.pdf [https://perma.cc/JVB6-XL3Q] (Exhibit 5).

(BIC), dolutegravir (DTG), elvitegravir (EVG), and raltegravir (RAL)), and two ritonavir (RTV) or cobicstat-boosted PIs (ataznavir (ATV) and darunavir (DRV)).[2]

45. While ART regimens can reduce the presence of HIV in the patient's bloodstream to extremely low levels, it does not eliminate HIV from the patient, and, thus, cannot cure an HIV infection.

46. An ART treatment regimen must be continuous and is lifelong. If adherence to an ART regimen is poor, the patient will see the viral load of HIV rise and can transmit HIV to others.

D. Truvada®

47. Truvada® is the trade name for a medication developed by Gilead for the treatment of HIV infections when used in combination with other antiretroviral drugs.

48. Truvada® is a fixed-dose combination of two well-known antiretroviral drugs: TDF and FTC. Approved for sale by the Food and Drug Administration (FDA) in 2004 for the treatment of HIV, Truvada® tablets are typically sold in an adult dosage of 300 mg TDF and 200 mg FTC.

49. TDF is a tenofovir prodrug, which means that it is not pharmacologically active when it is in the tablet form, but is chemically converted by metabolic processes in the body into tenofovir, the active pharmacological drug. Tenofovir is an NtRTI that was first discovered in the 1980s.[3]

[2] *See* HHS Panel on Antiretroviral Guidelines for Adults and Adolescents, *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV* 62–63, https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf [https://perma.cc/6UBG-TQDC] (last updated/reviewed July 10, 2019) (Exhibit 6).

[3] *See, e.g.*, U.S. Patent No. 4,808,716, https://patents.google.com/patent/US4808716A/en [https://perma.cc/SR9T-7ANJ] (Exhibit 7).

50. In the body, TDF is metabolized into tenofovir. It is then chemically altered (phosphorylated) inside human cells to tenofovir diphosphate, the compound that inhibits HIV reverse transcriptase.

51. Discovered in the mid-1990s, FTC is an NRTI that has long been used in ART regimens.[4]

52. When used for treatment of HIV-1, Truvada® is administered in combination with other antiretroviral agents in order to durably suppress HIV replication. Under current guidelines, a typical recommended ART regimen calling for administration of a daily Truvada® tablet would also include co-administration of an integrase inhibitor (for example, DTG or RAL). The FTC and TDF components of Truvada® are also sold as components of larger three- and four-drug Gilead products, including Atripla® (FTC/TDF/EFV), Complera® (FTC/TDF/RPV), and Stribild® (FTC/TDF/EVG/cobicistat). These products amount to once-daily ART regimens, where all the drugs are co-formulated into a single pill.

53. Gilead received FDA approval to sell Truvada®, in the same dosage form and strength approved for HIV-infection treatment, as a PrEP regimen in 2012.

E. Descovy®

54. Gilead also manufactures, distributes, and sells the antiretroviral drug Descovy® that, like Truvada®, includes both FTC and a tenofovir prodrug.

55. Unlike TDF in Truvada®, the tenofovir prodrug in Descovy® is tenofovir alafenamide fumarate (TAF). Like TDF in Truvada®, TAF is an ester of tenofovir that is metabolized into tenofovir in the body.

[4] *See* U.S. Patent No. 5,814,639, https://patents.google.com/patent/US5814639A/en [https://perma.cc/B4YK-T4GY] (Exhibit 8).

56. The FDA approved Descovy® in April 2016 for the treatment of HIV-1 infections when administered in combination with other antiretroviral drugs. Descovy® tablets are sold in a dosage of 200 mg FTC and 25 mg TAF.

57. On October 3, 2019, Gilead received FDA approval to sell Descovy®, in the same dosage form and strength approved for HIV-infection treatment, as a PrEP regimen, "excluding those who have receptive vaginal sex."[5]

F. Efforts to Develop Regimens to Prevent HIV Transmission

58. Although patients whose HIV is fully suppressed by ART receive a clinical benefit, there is also a public health benefit through the reduction of risk of transmission to HIV-negative persons. Poor adherence to the ART regimen, however, reduces these benefits. And persons not receiving ART or who are unaware of their HIV-positive status can still spread the virus. Thus, treatment of HIV as a way to prevent transmission is an incomplete solution.

59. Based on the limitations of ART, researchers generally pursue three separate and distinct biomedical strategies to protect HIV-negative persons from infection: (1) vaccines, (2) post-exposure prophylaxis, and (3) pre-exposure prophylaxis.

G. Decades of Unsuccessful Attempts to Create an HIV Vaccine

60. Since the discovery of HIV in the early 1980s, many researchers have sought a vaccine to prevent the spread of HIV and extensive research efforts are still devoted to vaccine development.

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[5] U.S. Food & Drug Admin., *FDA Approves Second Drug to Prevent HIV Infection as Part of Ongoing Efforts to End the HIV Epidemic*, FDA Newsroom: Press Announcements (Oct. 3, 2019) [hereinafter *FDA Approves Second Drug to Prevent HIV*], https://www.fda.gov/news-events/press-announcements/fda-approves-second-drug-prevent-hiv-infection-part-ongoing-efforts-end-hiv-epidemic [https://perma.cc/N3JP-M4NK] (Exhibit 9).

61. More money has been spent on the development of an HIV vaccine than any other vaccine in history. The WHO reports that "[t]he global investment on HIV vaccine research, including industry and research agencies in industrialized countries[,] has been estimated at approximately US$ 500 million per year."[6]

62. Today, the bulk of HIV-prevention funding is still directed to vaccines. In 2018, for example, AVAC, formerly the AIDS Vaccine Advocacy Coalition, reported that $1.14 billion was spent on HIV prevention research and development. Of that amount, 74 percent ($842 million) went to HIV vaccines, 12.3 percent ($140 million) to microbicides, and only 9.6 percent ($109 million) to PrEP efforts.[7]

63. While extensive research into an effective HIV vaccine continues, none presently exists.

H. Post-Exposure Prophylaxis (PEP) Regimens Based on Empirical Data

64. Another type of prevention regimen is known as post-exposure prophylaxis (PEP). PEP involves taking antiretroviral drugs shortly after a potential exposure that presents a substantial risk for HIV infection. Consistent with earlier guidance, present guidelines recommend administering drugs within 48-72 hours after exposure and remaining on the regimen for 28 days.[8]

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[6] World Health Organization, *HIV Vaccines*, https://www.who.int/hiv/topics/vaccines/Vaccines/en/ [https://perma.cc/4HMM-X27Z] (Exhibit 10).

[7] AVAC Resource Tracking for HIV Prevention Research & Development Working Group, *2018 HIV Prevention Research & Development Investments*, 6, 19, 24, 28 (July 2019), https://www.avac.org/resource/hiv-prevention-research-development-investments-2018-investing-end-epidemic [https://perma.cc/AQV5-BGL3] (Exhibit 11).

[8] Centers for Disease Control and Prevention, *Updated Guidelines for Antiretroviral Postexposure Prophylaxis After Sexual, Injection Drug Use, or Other Nonoccupational Exposure to HIV* (2016) [hereinafter Updated Guidelines], https://www.cdc.gov/hiv/pdf/programresources/cdc-hiv-npep-guidelines.pdf, [https://perma.cc/Q8UL-M32W] (Exhibit 12).

65. Because of ethical and logistical reasons, placebo-controlled, human clinical trials have not been performed to test the efficacy of different PEP regimens.[9] In the absence of such data, PEP recommendations have relied on preclinical animal studies that are limited to specific drugs and dosages and infection routes, observational data collected from the clinical follow-up of persons potentially exposed to HIV, and clinical experience from treating HIV-infected persons.

66. Following the approval of zidovudine (also known as azidothymidine or AZT) in 1987 as the first drug for treatment of HIV infections, one retrospective case-control study showed the odds of HIV infection among health care workers who took zidovudine prophylactically after an occupational exposure (e.g. needle-stick injuries) were reduced by approximately 81 percent.[10] The study cautioned that "[b]ecause it is difficult to control for known and unknown factors that contribute to HIV transmission, a retrospective case–control study is not the optimal design for assessing the efficacy of zidovudine; however, a prospective, placebo-controlled trial has not been possible."[11]

67. Over time, following the approval of new antiretroviral drugs and the availability of additional observational data, recommendations for PEP have evolved to focus on combination regimens, similar to those used to treat HIV-infected persons. However, the guidelines acknowledge that "the applicability of [combination ART recommendations] to PEP is unknown"

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[9] Dawn K. Smith et al., *Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States*, 54 CDC MORBIDITY AND MORTALITY WEEKLY REP. (RR02) 1, 2 (Jan. 21, 2005), https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5402a1.htm [https://perma.cc/8B8U-EY44] (Exhibit 13).

[10] Denise M. Cardo et al., *A Case–Control Study of HIV Seroconversion in Health Care Workers After Percutaneous Exposure*, 337 NEW ENG. J. MED. 1485, 1488 (1997), https://www.nejm.org/doi/10.1056/NEJM199711203372101 [https://perma.cc/88FM-2ZR8] (Exhibit 14).

[11] *Id*.

and that "[d]etermining which [antiretrovirtal drugs] and how many to use or when to alter a PEP regimen is primarily empiric."[12] Because of the lack of clinical trials, the precise effectiveness of PEP regimens remains unknown and, thus, none of the PEP regimens is FDA-approved for a PEP indication.

1. Early Data Regarding Tenofovir Alone for PEP

68. Early preclinical PEP data from animal models relate solely to work with tenofovir alone, either injected under the skin (subcutaneously) or topically applied (*e.g.*, vaginally). No data were generated for the later-approved TDF. And the tenofovir data were decidedly mixed. Accordingly, at the time of CDC's patented PrEP research, there were no relevant preclinical data regarding the administration of the FTC/TDF combination for PEP, and like all PEP regimens, there were no human clinical data.

69. In 1998, for example, a preclinical animal study was published regarding the use of subcutaneous tenofovir alone in a PEP regimen. In that study, administration of subcutaneous tenofovir to macaque monkeys after intravenous viral exposure for four weeks prevented 100

[12] Adelisa L. Panlilio et al., *Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis*, 54 CDC MORBIDITY AND MORTALITY WEEKLY REP. (RR-9) 1, 5 (Sept. 30, 2005), https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5409a1.htm [https://perma.cc/EE6Y-A6DP] (Exhibit 15).

percent of infections.[13] However, the PEP regimens did not prevent infections when the regimens were started at 48 hours after exposure or when the duration of treatment was ten days or less.[14]

2. PEP Guidelines

70. In 1996, the first U.S. Public Health Service (PHS) recommendations for the use of PEP after occupational exposure to HIV were published. The fourth update to those recommendations, "Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis," was published on September 30, 2005.[15] Also in 2005, HHS published recommendations on "Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV."[16]

71. These 2005 guidelines indicate that Truvada® as an FTC/TDF regimen was only one of numerous PEP regimens that could be selected based on a variety of factors.

72. For occupational exposure (*e.g.*, needle-stick injuries in health care providers), eight different basic treatment regimens, the guidelines recommended seven expanded treatment regimens, and one injection antiviral (enfuvirtide), depending on the type and severity of the exposure. Two-drug treatment regimens were recommended for low-risk exposures and three (or four) drug regimens for increased-risk exposures:[17]

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[13] Che-Chung Tsai et al., *Effectiveness of Postinoculation (R)-9-(2-phosphonylmethoxypropyl) Adenine Treatment for Prevention of Persistent Simian Immunodeficiency Virus SIV$_{mne}$ Infection Depends Critically on Timing of Initiation and Duration of Treatment*, 72 J. VIROLOGY (5) 4265, 4271 (1998), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC109656/ [https://perma.cc/XLG8-RA22] (Exhibit 16); *see also* Ron A. Otten et al., *Efficacy of Postexposure Prophyaxis After Intravaginal Exposure of Pig Tailed Macaques to a Human-Derived Retrovirus (Human Immunodeficiency Virus Type 2)*, 74 J. VIROLOGY (20) 9771 (2000), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC112413/ [https://perma.cc/K6V8-XK4F] (Exhibit 17).

[14] Tsai et al., *supra* note 13, at 4271.

[15] Panlilio et al., *supra* note 12.

[16] Smith et al., *supra* note 9.

[17] Panlilio et al., *supra* note 12, at Appendix (emphasis added).

- Zidovudine (Retrovir™; ZDV; AZT) plus lamivudine (Epivir®; 3TC); available as Combivir™
- Zidovudine (Retrovir®; ZDV; AZT) plus emtricitabine (Emtriva™; FTC)
- Tenofovir DF (Viread®; TDF) plus lamivudine (Epivir®; 3TC)
- **Tenofovir DF (Viread®; TDF) plus emtricitabine (Emtriva™; FTC); available as Truvada®**
- Lamivudine (Epivir®; 3TC) plus stavudine (Zerit®; d4T)
- Emtricitabine (Emtriva™; FTC) plus stavudine (Zerit®; d4T)
- Lamivudine (Epivir®; 3TC) plus didanosine (Videx®; ddI)
- Emtricitabine (Emtriva™; FTC) plus didanosine (Videx®; ddI), or
- Any of the above plus one of the following:
    - Lopinavir/ritonavir (Kaletra®; LPV/RTV)
    - Atazanavir (Reyataz®; ATV) with or without ritonavir (Norvir®; RTV)
    - Fosamprenavir (Lexiva®; FOSAPV) with or without ritonavir (Norvir®; RTV)
    - Indinavir (Crixivan®; IDV) with or without ritonavir (Norvir®; RTV)
    - Saquinavir (Invirase®; SQV) plus ritonavir (Norvir®; RTV)
    - Nelfinavir (Viracept®; NFV)
    - Efavirenz (Sustiva®; EFV)

73. For nonoccupational exposure (*e.g.*, sexual exposure), the 2005 guidelines recommended eleven different treatment regimens, depending on the type and timing of the exposure:[18]

- [Preferred] Efavirenz plus (lamivudine or emtricitabine) plus (zidovudine or tenofovir)

[18] Smith et al., *supra* note 9, at 9 tbl.2.

- [Preferred] Lopinavir/ritonavir (co-formulated as Kaletra®) plus (lamivudine or emtricitabine) plus zidovudine
- [Alternative] Efavirenz plus (lamivudine or emtricitabine) plus abacavir or didanosine or stavudine
- [Alternative] Atazanavir/ritonavir plus (lamivudine or emtricitabine) plus (zidovudine or stavudine or abacavir or didanosine) or tenofovir
- [Alternative] Fosamprenavir plus (lamivudine or emtricitabine) plus (zidovudine or stavudine) or (abacavir or tenofovir or didanosine)
- [Alternative] Fosamprenavir/ritonavir plus (lamivudine or emtricitabine) plus (zidovudine or stavudine or abacavir or tenofovir or didanosine)
- [Alternative] Indinavir/ritonavir plus (lamivudine or emtricitabine) plus (zidovudine or stavudine or abacavir or tenofovir or didanosine)
- [Alternative] Lopinavir/ritonavir (co-formulated as Kaletra) plus (lamivudine or emtricitabine) plus (stavudine or abacavir or tenofovir or didanosine)
- [Alternative] Nelfinavir plus (lamivudine or emtricitabine) plus (zidovudine or stavudine or abacavir or tenofovir or didanosine)
- [Alternative] Saquinavir/ritonavir plus (lamivudine or emtricitabine) plus (zidovudine or stavudine or abacavir or tenofovir or didanosine)
- [Alternative] Abacavir plus lamivudine plus zidovudine

74. As indicated, the FTC/TDF Truvada® combination is only listed as one of many possible combinations in the 2005 occupational guidelines. FTC and tenofovir are listed as parts of several of the eleven PEP regimens in the 2005 nonoccupational guidelines (which would apply to sexual exposures), but only in further combination with at least one additional drug.

75. The 2005 guidelines explain that selection of a regimen should involve the empiric evaluation of several factors, namely (1) severity of the exposure and imminent need for PEP treatment, (2) toxicity and side effects of the antiretroviral drugs, (3) the likelihood of developing viral resistance to those drugs, and (4) potential of non-compliance to a regimen. In this vein, the occupational guidelines state, for example, that "[a]lthough use of a three- (or more) drug regimen

might be justified for exposures that pose an increased risk for transmission, whether the potential added toxicity of a third or fourth drug is justified for lower-risk exposures is uncertain, especially in the absence of data supporting increased efficacy of more drugs in the context of occupational PEP."[19]

76. Today, the prevailing 2016 HHS PEP guidelines recommend a triple-drug combination of HIV drugs within 48 to 72 hours of a possible exposure and staying on the daily regimen for a month. Unlike earlier guidelines, the present guidelines recommend Truvada® as part of a three-drug combination for PEP. The 2016 guidelines do not recommend administration of Truvada® alone or Descovy® alone for PEP.[20]

I. Pre-Exposure Prophylaxis (PrEP)

77. Lacking a vaccine or another pre-exposure preventive drug regimen, some researchers sought oral medications that, when taken on a regular basis prior to exposure, prevent the spread of HIV. This type of preventive regimen is known as pre-exposure prophylaxis (PrEP).

78. "Unlike PEP, which is a 28-course of antiretroviral therapy taken shortly after a high-risk exposure, PrEP refers to HIV-negative individuals taking a daily dose of antiretroviral therapy started before HIV exposure and continuing throughout periods of risk."[21] "PEP may be challenging to implement effectively in humans because of the difficulty individuals have in self-identifying high-risk exposures and the numerous operational challenges in providing PEP to patients as soon as possible after high-risk exposure. In contrast to PEP, PrEP dosing is unlinked

[19] Panlilio et al., *supra* note 12, at 5 ("Selection of HIV PEP Regimens").
[20] Updated Guidelines, *supra* note 8, at 31 tbl.5.
[21] Albert Y. Liu, et al., *Preexposure Prophylaxis for HIV: Unproven Promise and Potential Pitfalls*, 296 JAMA (7) 863, 863 (2006), https://jamanetwork.com/journals/jama/fullarticle/203155 [https://perma.cc/C2SQ-8PXQ] (Exhibit 18).

to sexual practice, does not require individuals to identify high-risk exposures, and does not need to be initiated within a critical period after exposure."[22]

79. Also, PrEP regimens, in contrast to PEP regimens, have been supported by specific animal data and randomized, placebo-controlled human clinical trials of specific regimens (like Truvada for PrEP®) in order to be approved by FDA and similar regulatory organizations worldwide.

80. Evidence from several large clinical trials and observational studies of at-risk populations estimate the effectiveness of Truvada for PrEP® at approximately 99 percent.[23] On information and belief, Gilead has generated similar data and estimates for Descovy® for PrEP in successfully seeking FDA approval for that regimen.[24]

1. Early PrEP Efforts

81. Prior to CDC's establishment of effective daily PrEP regimens in the mid-2000s, concerns existed about the safety, cost, and effectiveness of potential regimens. In particular, concerns existed regarding PrEP's overall efficacy, "risk compensation" (a person using PrEP increasing risky behavior because they perceive themselves at lower risk), a person's ability to adhere to a daily PrEP regimen, the safety and cost of a daily PrEP regimen for otherwise healthy people, and the potential for developing resistant HIV strains if PrEP fails. Each of these concerns could impact both the effectiveness of a PrEP regimen as well as the future spread of HIV.

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[22] *Id*.

[23] Centers for Disease Control and Prevention, *Effectiveness of Prevention Strategies to Reduce the Risk of Acquiring or Transmitting HIV*, CDC.gov [hereinafter *Effectiveness of Prevention Strategies*], https://www.cdc.gov/hiv/risk/estimates/preventionstrategies.html [https://perma.cc/3SSR-XM4V] (last updated/reviewed July 18, 2019) (Exhibit 19).

[24] U.S. Food & Drug Admin., *FDA Briefing Document: Meeting of the Antimicrobial Drugs Advisory Committee*, FDA.gov (Aug. 7, 2019), https://www.fda.gov/media/129607/download [https://perma.cc/H2EP-J68N] (Exhibit 20).

82. Early efforts to develop PrEP regimens were focused on administration of subcutaneous tenofovir. In the mid-1990's, high doses of subcutaneous tenofovir alone had been shown to have prophylactic activity in macaques exposed intravenously to simian immunodeficiency virus (SIV), a virus similar to HIV, and frequently modified to contain parts of the HIV genome, a virus referred to as simian HIV (SHIV).[25]

83. Subsequent tests also showed protection with subcutaneous tenofovir when newborn macaques were injected with one dose of tenofovir four hours before and one dose of tenofovir 24 hours after oral inoculation with SIV.[26] The same researchers, however, found less than complete protection when using a lower dose of tenofovir, but the same two-dose regimen.[27] Likewise, in a third study, those same researchers found that a single dose of subcutaneous tenofovir administered to pregnant macaques did not protect newborns against oral SIV and intravenous SHIV inoculations after birth.[28]

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[25] *See* Che-Chung Tsai et al., "Prevention of SIV Infection in Macaques by (R)-9-(2-phosohonyl-methoxypropyl)adenine," 270 SCIENCE 1197, 1199 (1995), https://science.sciencemag.org/content/270/5239/1197 [https://perma.cc/QL2B-8S9T] (Exhibit 21).

[26] *See* Koen K.A. Van Rompay et al., *Two Doses of PMPA Protect Newborn Macaques Against Oral Simian Immunodeficiency Virus Infection*, 12 AIDS F79, F81–82 (1998), https://journals.lww.com/aidsonline/pages/articleviewer.aspx?year=1998&issue=09000&article=00001&type=fulltext#pdf-link [https://perma.cc/7L97-7PLF] (Exhibit 22).

[27] *See* Koen K.A. Van Rompay et al., *Two Low Doses of Tenofovir Protect Newborn Macaques Against Oral Simian Immunodeficiency Virus Infection*, 184 J. INFECTIOUS DISEASES 429, 434–35 (2001), https://academic.oup.com/jid/article/184/4/429/808643 [https://perma.cc/B9FJ-U6RL] (Exhibit 23).

[28] *See* Koen K.A. Van Rompay et al., *Administration of 9-[2-(phosphonomethyl)propyl]adenine (PMPA) for Prevention of Perinatal Simian Immunodeficiency Virus Infection in Rhesus Macaques*, 14 AIDS RES. & HUM. RETROVIRUSES 761, 764–66 (1998), https://www.liebertpub.com/doi/abs/10.1089/aid.1998.14.761 [https://perma.cc/8PBK-QDGB] (Exhibit 24).

84. In the early to mid-2000s, researchers continued to evaluate subcutaneous tenofovir, TDF (which received FDA approval in 2001) and TAF, also known as GS-7340,[29] as single-drug regimens to prevent SIV infection (modeling HIV infection).

85. But those efforts were, like clinical PrEP efforts generally in the early to mid-2000s, surrounded with skepticism, uncertainty, and a general lack of data.

86. For example, in November 2004, the Center for HIV Identification, Prevention, and Treatment Services published an article titled, "Anticipating the Efficacy of HIV Pre-exposure Prophylaxis (PrEP) and the Needs of At-Risk Californians" (Szekeres).[30] The authors stated:

> It is not yet known whether PrEP is a safe or effective approach to HIV prevention, however, as studies for its evaluation in several populations are just preparing to begin. These planned studies and future, yet-to-be-planned clinical trials will determine whether and to what degree PrEP is safe and effective.[31]

87. Szekeres specifically reported that interest existed in 2004 for oral TDF-only regimens. It references and discusses six then-nascent human studies (in Africa, Thailand, and the United States) designed to investigate the safety and efficacy of TDF-only for PrEP.[32] No other PrEP regimens are discussed.

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[29] *See, e.g.*, Koen K.A.Van Rompay et al., *Evaluation of Oral Tenofovir Disoproxil Fumarate and Topical Tenofovir GS-7340 to Protect Infant Macaques Against Repeated Oral Challenges with Virulent Simian Immunodeficiency Virus*, 43 J. ACQUIRED IMMUNE DEFICIENCY SYNDROME 6 (2006), https://journals.lww.com/jaids/fulltext/2006/09000/Evaluation_of_Oral_Tenofovir_Disoproxil_Fumarate.2.aspx#pdf-link [https://perma.cc/MTP8-D8YR] (Exhibit 25).

[30] Greg Szekeres et al., *Anticipating the Efficacy of HIV Pre-Exposure Prophylaxis (PrEP) and the Needs of At-Risk Californians*, CENTER FOR HIV IDENTIFICATION, PREVENTION, AND TREATMENT SERVICES (2004), http://www.uclaisap.org/documents/PreP_Report_FINAL_11_1_04.pdf [https://perma.cc/3XJ3-9XHK] (Exhibit 26).

[31] *Id.* at 3.

[32] *Id*. at 6–10.

88. In 2006, a group of CDC researchers, including inventors Drs. Ronald Otten, Robert Janssen, and Thomas Folks, and led by Dr. Shambavi Subbarao, published the first preclinical PrEP study on the use of oral TDF alone in macaque models subjected to repeated rectal viral exposures.[33] While the article was received for publication in January 2006, the study results were available to CDC researchers and others in the field prior to the patented research.

89. The Subbarao study showed that oral TDF produced results far less positive than those seen with subcutaneous tenofovir in earlier studies. Specifically, while infection with SHIV was delayed, even macaques receiving TDF daily became infected "after a median duration of [six] to [seven] weeks."[34] The study concluded that "[t]hese data demonstrate that treatment with oral TDF provided partial protection against SHIV infection but ultimately did not protect all TDF treated animals against multiple virus challenges."[35]

90. Similarly, a study co-sponsored by Gilead and the Government had shown that oral TDF demonstrated lower efficacy in infant macaques exposed orally to SIV.[36]

91. Based on these results, no one in the field expected a tenofovir prodrug in combination with FTC, or any other type of PrEP regimen, to have the superior effectiveness that the FTC/tenofovir prodrug regimens are known to have today.

92. Nevertheless, researchers during the mid-2000s continued to focus on developing vaccines or TDF-only regimens for PrEP (as seen in the ongoing clinical trials). Prior to CDC's

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[33] *See* Shambavi Subbarao et al., *Chemoprophylaxis with Tenofovir Disoproxil Fumarate Provided Partial Protection Against Infection with Simian Immunodeficiency Virus in Macaques Given Multiple Virus Challenge*s, 194 J. INFECTIOUS DISEASES 904 (2006), https://academic.oup.com/jid/article/194/7/904/862971 [https://perma.cc/H98P-T9QL] (Exhibit 27).

[34] *Id*. at 904.

[35] *Id.*

[36] Van Rompay et al., *supra* note 29 at 12.

patented work, no preclinical or clinical PrEP studies during the mid-2000s were conducted using the combination of FTC and TDF (or TAF). Only the CDC researchers focused their studies on a two-drug regimen.

2. Research Leading to CDC's Innovative FTC/Tenofovir Prodrug Regimens

93. By 2004, researchers at CDC's Division of HIV/AIDS Prevention had begun designing experiments to administer FTC and a tenofovir prodrug (or tenofovir) in combination as potential PrEP regimens to prevent HIV infection in persons at high risk.

94. The impetus for CDC's efforts was to improve the TDF-only regimens that had been proven insufficiently protective (and less protective than subcutaneous tenofovir) by the research of Dr. Subbarao and others. While many researchers aware of the results of Dr. Subbarao's study continued to pursue single-drug regimens (such as the TDF-only clinical trials), the CDC researchers pursued a different direction and contemplated that the combination of TDF and FTC could result in new, more effective PrEP regimens.

95. While two-drug regimens would generally be considered more toxic, the CDC researchers hypothesized that the inclusion of FTC—as an effective antiretroviral drug with relatively low toxicity—could add more protection than seen with TDF alone. The CDC researchers were the first group to take the innovative FTC/tenofovir prodrug combination path in PrEP preclinical or clinical studies.

3. CDC's Animal Modeling Techniques

96. CDC's breakthrough work was enabled in part by a new and precise animal modeling method that better simulates human HIV infections.

97. In prior animal research on HIV treatment and transmission, SIV or SHIV was typically introduced into macaque (or other primate) models in a single high dose at mucosal surfaces such that most, if not all, of the macaques would acquire an infection that could cause a

disease similar to AIDS. This methodology did not accurately represent the type of repeat, low-dose mucosal exposures experienced by humans with the sexual transmission of HIV, and thereby could underestimate efficacy.

98. Under CDC's new methodology, the virus was painstakingly administered into rhesus macaques in repeated and precise low doses, by applying it vaginally or rectally, with the intent to more accurately model the conditions by which HIV is sexually transmitted in humans. In addition, the CDC researchers used a SHIV that incorporated and expressed the type of envelope (exterior) of HIV-1, which also better simulated human HIV transmission.

4. CDC's Determination of Proper Dosing

99. The precision of CDC's experimental design, in terms of simulating and modeling the exposure of human at-risk persons who were likely to benefit from the proposed PrEP regimens, was also enabled by the inventors' prior determination of the proper doses of FTC and TDF used in their study.

100. Given that Truvada® was a commercially available and FDA-approved product for HIV treatment, the researchers sought to mirror Truvada® HIV-treatment doses in the macaques, as it could be PrEP regimens that the FDA would likely approve more quickly. Nevertheless, at the time, no literature or other studies suggested that the therapeutic doses of TDF and FTC available in Truvada® would also constitute effective preventive doses for a PrEP regimen.

101. As smaller mammals, macaques were known to eliminate drugs faster than humans. Thus, even before starting to model human dosages, the researchers had to conduct in-depth pharmacokinetic[37] studies to determine what doses in macaques would achieve appropriate blood and cellular levels of FTC and TDF in humans.

[37] "Pharmacokinetics" chiefly refers to the movement of drugs into, through, and out of the human body.

5. CDC's Determination of Appropriate FTC Dose

102. At the time of CDC's research, very little pharmacokinetic data were available for FTC in macaques. Accordingly, in late December 2004, Dr. Walid Heneine of the CDC research team emailed Gilead employees, including Drs. Michael Miller and Howard Jaffe, about executing a Material Transfer Agreement (MTA) to obtain FTC and also to seek "any suggestions" Gilead had regarding pharmacokinetic studies in macaques "that would help define the best FTC concentration to use in macaques."[38]

103. Ultimately, Gilead executed a 2004 MTA to provide FTC to CDC, but did not provide any of the requested pharmacokinetic data. Instead, Gilead's Dr. Miller directed Dr. Heneine to a third party for such data, and agreed that Dr. Heneine's suggestion that a 20 mg/kg dose of FTC was "a good one."[39]

104. Accordingly, the CDC researchers proceeded with a pharmacokinetic study to determine the appropriate FTC dose for the macaques.

105. To determine the appropriate FTC dose, six macaques were separately administered 48, 30, 20, 16, 15, or 12 mg/kg FTC orally and their drug levels measured at 1, 2, 4, 8, and 24 hour intervals. The research found that an FTC dose in macaques of 20 mg/kg was comparable to the 200 mg FTC dose in humans taking a daily Truvada® tablet.

6. CDC's Determination of Appropriate TDF Dose

106. The CDC researchers were already aware of a number of studies conducted on dosing of TDF in rhesus macaques, including Dr. Subbarao's TDF study. Nonetheless, the CDC researchers again conducted their own pharmacokinetic research to ensure proper dosing.

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[38] E-mail chain between Dr. Walid Heneine and Drs. Howard Jaffe and Michael Miller (December 21–22, 2004) (Exhibit 28).
[39] *Id.*

107. To determine the appropriate oral TDF dose, five macaques were orally administered 15, 20, 24, 37, or 46 mg/kg of TDF and their drug levels measured at the same hourly intervals used for the FTC portion of the study.

108. The researchers determined that a TDF dose of between 20 to 24 mg/kg in macaques resulted in blood levels of tenofovir within the range of those seen in humans taking a daily tablet of Truvada®.[40]

109. The CDC researchers decided to proceed with the 22mg/kg dose within that range.[41]

7. CDC's PrEP Experiments

110. The animal experiments of the CDC-designed study began in May 2005, with PrEP regimens featuring FTC, subcutaneous tenofovir, and oral TDF tested against rectal SHIV exposures. The experiments involved 33 macaques, which were divided into four drug-treatment groups and one control group.

111. Six macaques were placed into each of the four groups that were prophylactically treated with either: (i) subcutaneously injected FTC alone (Group 1); (ii) orally administered FTC and TDF with food (Group 2); (iii) subcutaneously administered FTC and a higher dose of tenofovir (Group 3); or, (iv) intermittently and subcutaneously administered FTC and tenofovir (Group 4). Groups 1, 2 and 3 received the prescribed drug regimen daily. Group 4 only received drugs within a 26-hour period surrounding SHIV exposure, with a first administration occurring two hours before and a second administration 24 hours after the exposure.

112. No drugs were administered to the one control group of 18 macaques. Of these macaques, nine were part of this study and nine were historical controls from earlier studies performed under identical conditions.

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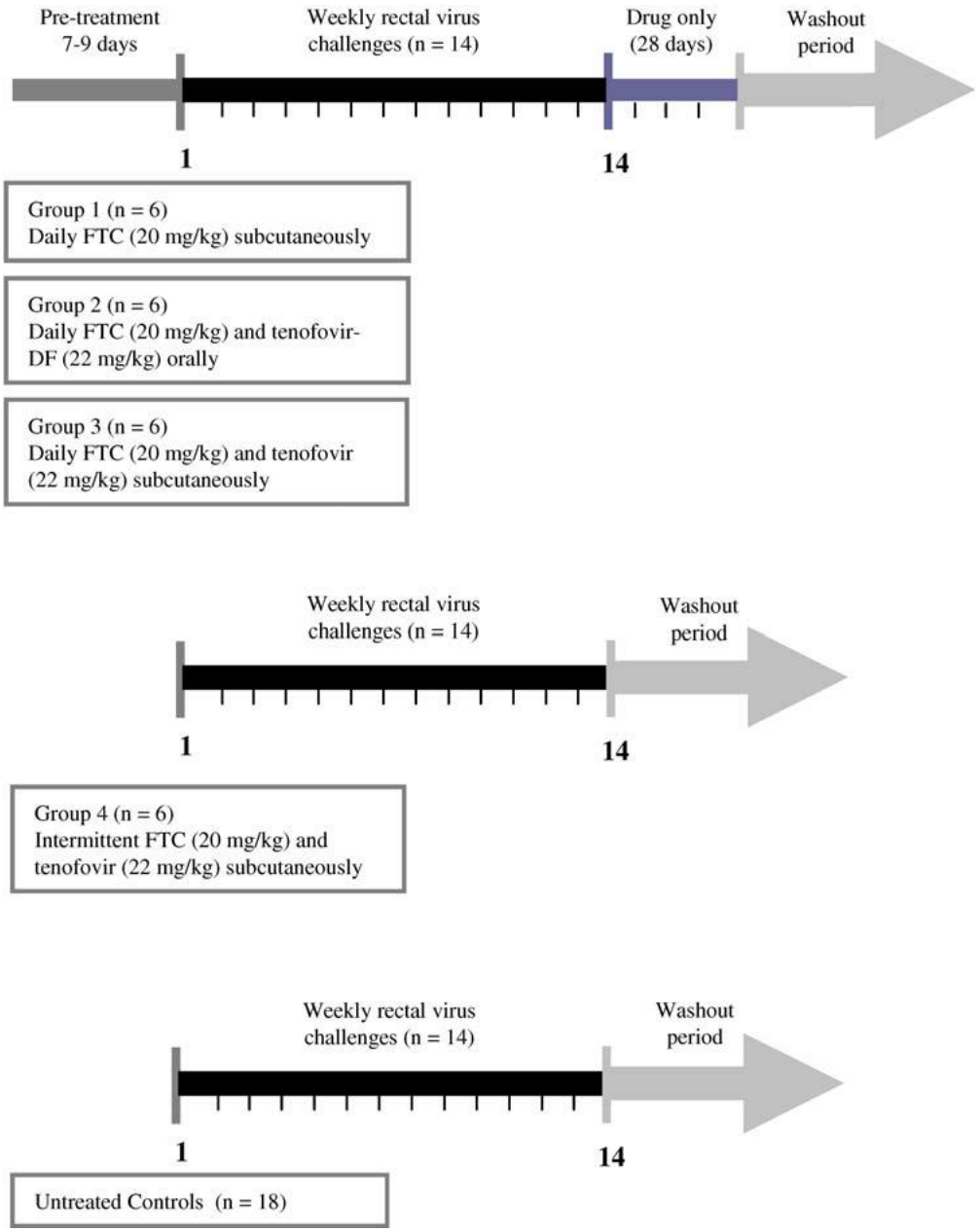
[40] García-Lerma et al., *infra* note 49, at 294.
[41] *Id*.

113. Using CDC's newly developed modeling techniques, each macaque in the study was challenged (exposed) rectally with SHIV beginning seven to nine days after the initial treatment. Rather than being challenged with one large dose, a smaller dose was repeated once a week. That dosage routine modeled conditions under which at-risk humans are often exposed to HIV (in viral levels and conditions) when the virus is transmitted sexually in humans.

114. Each SHIV exposure occurred two hours after drug treatments and continued weekly (one exposure per week) for 14 weeks, unless an animal contracted a SHIV infection. After the 14 weeks, drug treatments continued for another 28 days. Infected animals were then monitored for several additional months to measure viral plasma levels and drug resistance. This protocol is summarized in the figure below:[42]

[42] *Id*. at 293 fig.1.

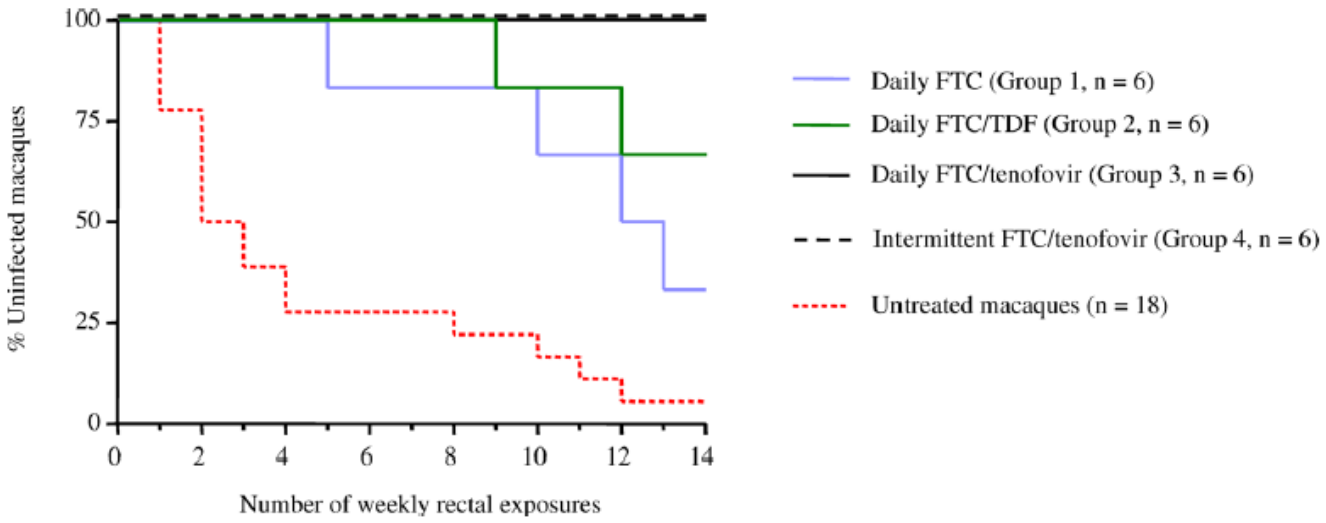


8. Results of CDC's PrEP Experiments

115. The test results demonstrated that both daily and intermittent dosing of FTC plus TDF (or subcutaneous tenofovir) prior to exposure were unexpectedly effective in protecting against the transmission of an immunodeficiency retrovirus (SHIV). The risk of infection in Group 2 was 7.8 times lower than in untreated control macaques. And all macaques in Groups 3 and 4

were protected from infection. These results demonstrated the extremely high efficacy of PrEP regimens consisting of sufficient doses of FTC and tenofovir (or a prodrug of tenofovir).

116. These results are represented graphically in the figure below:[43]



117. Collectively, the results demonstrated that a person at risk for HIV infection could be effectively protected against HIV infection by regular prophylactic doses of FTC and tenofovir or FTC and a tenofovir prodrug. From these results, the CDC researchers were also able to conclude that dosing levels of 200 mg of FTC and 300 mg of TDF would be highly effective in adult humans.

118. These results also demonstrate that the CDC researchers are the true and correct inventors of the FTC/tenofovir prodrug regimens for effective prevention of HIV infections claimed in the Patents-in-Suit. Accordingly, Gilead's public statement that the Government "did not invent . . . Truvada® for PrEP"[44] is misleading.

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[43] *Id*. at 295 fig.2.

[44] *Gilead Science Statement On Inaccurate Reporting on Truvada®*, Gilead.com, (May 14, 2019) [hereinafter *Gilead Statement*], https://www.gilead.com/news-and-press/company-statements/gilead--sciences--statement--on--inaccurate--reporting--on--truvada [https://perma.cc/6QQ4-7Z7X] (Exhibit 29).

J. Gilead's Contribution Limited to Drug Donations

119. Gilead's involvement in the patented research was limited to the donation of study drugs.

120. Under several MTAs with CDC, signed during the period from 2004 to 2008, Gilead provided the FTC, TDF, and tenofovir used in CDC's research.

121. The earliest MTA related to the research leading to the Patents-in-Suit was signed in December 2004 by Dr. Heneine, and later by Dr. Mick Hitchcock, Gilead's then Vice President of Medical Affairs, in response to Dr. Heneine's email request for a transfer of FTC to CDC.[45]

122. Ultimately, several additional MTAs were signed relating to transfers of drugs used in CDC's patented research. All contained substantially identical terms regarding handling of the study data as well as the disclosure, patenting, and licensing of inventions resulting from CDC's work.

123. For example, the 2004 MTA states that CDC, as the recipient of the drug, would "promptly disclose to Provider [Gilead] all results, data, and other information or materials derived from" any materials and confidential information provided by Gilead. CDC further agreed "to promptly notify Provider of any Inventions."[46]

124. In turn, Gilead agreed that the FDA, the National Institutes of Health (NIH), and CDC (collectively identified in the MTA as the Public Health Service (PHS)) would "retain title to any patent or other intellectual property rights in inventions made by its employees in the course of the Research Project."[47] The 2004 MTA further states that "PHS agrees to give serious and

[45] Public Health Service Material Transfer Agreement Between Centers for Disease Control and Prevention and Gilead Sciences, Inc. (executed Jan. 31, 2005) (Exhibit 30).
[46] *Id*. at 8.
[47] *Id*.

reasonable consideration to Provider's request for a non-exclusive or exclusive license on commercially reasonable terms under PHS's intellectual property rights in or to any Inventions." Gilead further agreed to use any research results from CDC "solely for internal research purposes."[48] The other relevant MTAs contain the same provisions.

125. As described herein, CDC complied with its obligations under all of the relevant MTAs, by *inter alia*, frequently disclosing to Gilead (and the public) that it had filed a patent application on its research, and repeatedly inviting Gilead, over later years, to license the issued patents.

126. Other than the provision of the study drugs, Gilead provided no substantive input into the protocol and methods used in CDC research. Accordingly, when CDC's results were published in a February 2008 issue of the *PLoS Medicine* journal (the 2008 PLoS article),[49] no Gilead personnel were named as co-authors. Instead, the article simply thanked "[James] Rooney and colleagues from Gilead for providing the drugs . . . ."[50]

127. Gilead's lack of involvement in the CDC research mirrored its lack of interest in CDC's patented work and in PrEP generally at that time.[51]

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[48] *Id*.

[49] *See* J. Gerardo García-Lerma et al., *Prevention of Rectal SHIV Transmission in Macaques by Daily or Intermittent Prophylaxis with Emtricitabine and Tenofovir*, 5 PLoS MEDICINE (2) 291 (2008), https://journals.plos.org/plosmedicine/article/file?id=10.1371/journal.pmed.0050028&type=printable [https://perma.cc/GB53-28MB] (Exhibit 31).

[50] *Id*. at 298.

[51] *HIV Prevention Drug: Billions in Corporate Profits After Millions in Taxpayer Investments: Hearing Before the H. Comm. on Oversight and Reform*, 116th Cong. 5 (2019) [hereinafter *H. Comm. Hearing*] (statement of Dr. Robert M. Grant, Professor of Medicine, University of California, San Francisco), https://www.govinfo.gov/content/pkg/CHRG-116hhrg36660/pdf/CHRG-116hhrg36660.pdf [https://perma.cc/M5KY-YPFP] (Exhibit 32). *See also House Oversight and Reform Committee Hearing on HIV Prevention Drug: Billions in Corporate Profits After Millions in Taxpayer Investments*, Bloomberg Government (May 17,

K. Patent Applications Covering CDC's Invention and Disclosure to Gilead

128. A provisional patent application (2006 Provisional Application) based on CDC's research was filed on February 3, 2006 with the U.S. Patent and Trademark Office (PTO). Subsequently, a non-provisional application (Application No. 11/669,547) was filed on January, 31, 2007, and was published by the PTO on November 15, 2007.

129. An international patent application on the same subject matter, PCT Application No. US2007/002926, was published on August 16, 2007.

130. The cover page of the 2008 PLoS article has a listing entitled "Competing Interests," which discloses that several CDC authors "are named in a U.S. Government patent application related to methods for HIV prophylaxis."[52] By the time the article was received by the journal for publication on June 6, 2007, both the U.S. provisional and nonprovisional patent applications had been filed with the PTO.

131. On February 1, 2008, Dr. Heine emailed a draft of the article (including the "Competing Interests" section) was emailed to Drs. James Rooney and William Lee of Gilead.

132. Later papers relating to the same CDC research were similarly made available to Gilead for review before publication.

133. For example, between 2010 and 2016, at least eleven such CDC-authored publications identified the same pending Government patent application, in a manner similar to the 2008 PLoS article.[53]

2019) [hereinafter Bloomberg Transcript] (Exhibit 33); *Price of HIV Prevention Drug Truvada*, C-SPAN (May 16, 2019), https://www.c-span.org/video/?460810-1/gilead-ceo-daniel-oday-testifies-truvada-hiv-prevention-drug-pricing.

[52] García-Lerma et al., *supra* note 49, at 291.

[53] *See* J. Gerardo García-Lerma et al., *Intermittent Prophylaxis with Oral Truvada Protects Macaques from Rectal SHIV Infection*, 2 SCI. TRANSLATIONAL MED. (14ra4) 1 (2010), https://stm.sciencemag.org/content/2/14/14ra4.long [https://perma.cc/2ZFG-ST3Y] (Exhibit 34)

134. By providing these papers, CDC repeatedly made Gilead aware of the Government's filing of a patent application in 2006 and the Government's subsequent research efforts.

(finding PrEP regimens with same drugs to be protective); J. Gerardo García-Lerma & Walid Heneine, *Animal Models of Antiretroviral Prophylaxis for HIV Prevention*, 7 CURRENT OPINION HIV & AIDS (6) 505 (2012), https://journals.lww.com/co-hivandaids/Abstract/2012/11000/Animal_models_of_antiretroviral_prophylaxis_for.4.aspx [https://perma.cc/8NJ3-YFKL] (Exhibit 35); Jessica Radzio et al., *Prevention of Vaginal SHIV Transmission in Macaques by a Coitally-Dependent Truvada Regimen*, 7 PLoS One (12) 1 (2012), https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0050632 [https://perma.cc/9F9H-5E24] (Exhibit 36); Mian-er Cong et al., *Prophylactic Efficacy of Oral Emtricitabine and Tenofovir Disoproxil Fumarate Combination Therapy Against a Tenofovir-Resistant Simian/Human Immunodeficiency Virus Containing the K65R Mutation in Macaques*, 208 J. INFECTIOUS DISEASES 463 (2013), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3699008/ [https://perma.cc/LZB9-JQWF] (Exhibit 37); Jessica Radzio et al., *Depot-Medroxyprogesterone Acetate Does Not Reduce the Prophylactic Efficacy of Emtricitabine and Tenofovir Disoproxil Fumarate in Macaques*, 67 J. ACQUIRED IMMUNE DEFICIENCY SYNDROME (4) 365 (2014), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4213266/ [https://perma.cc/VK4C-GZLV] (Exhibit 38); Charles Dobard et al., *Postexposure Protection of Macaques from Vaginal SHIV Infection by Topical Integrase Inhibitors*, 6 SCI. TRANSLATIONAL MED. (227ra35) 1 (2014), https://stm.sciencemag.org/content/6/227/227ra35.long [https://perma.cc/FN65-ZYSQ] (Exhibit 39); Ivana Massud et al., *Pharmacokinetic Profile of Raltegravir, Elvitegravir and Dolutegravir in Plasma and Mucosal Secretions in Rhesus Macaques*, 70 J. ANTIMICROBIAL CHEMOTHERAPY 1473 (2015), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4398473/ [https://perma.cc/2WYP-KJUV] (Exhibit 40); Peter L. Anderson et al., *Nondaily Preexposure Prophylaxis for HIV Prevention*, 11 CURRENT OPINION HIV & AIDS 94 (2016), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4784976/ [https://perma.cc/TJ8Y-YMTE] (Exhibit 41); Susan Ruone et al., *HIV-1 Evolution in Breakthrough Infections in a Human Trial of Oral Pre-exposure Prophylaxis with Emtricitabine and Tenofovir Disoproxil Fumarate*, 72 J. ACQUIRED IMMUNE DEFICIENCY SYNDROME (2) 129 (2016), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4876572/ [https://perma.cc/TD25-MGRH] (Exhibit 42); Mian-er Cong et al., *Antiretroviral Drug Activity in Macaques Infected During Pre-Exposure Prophylaxis Has a Transient Effect on Cell-Associated SHIV DNA Reservoirs*, 11 PLOS ONE (11), 1 (Nov. 2, 2016), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5091888/, *archived at* https://perma.cc/443Z-YFEA (Exhibit 43); Jessica Radzio et al., *Combination Emtricitabine and Tenofovir Disoproxil Fumarate Prevents Vaginal Simian/Human Immunodeficiency Virus Infection in Macaques Harboring* Chlamydia Trachomatis *and* Trichomonas Vaginalis, 213 J. INFECTIOUS DISEASES 1541 (2016), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4837911/ [https://perma.cc/ZK6P-P5GH] (Exhibit 44).

L. Immediate Impact of CDC's Innovative Regimens on Clinical Research

135. Results from CDC's research were first presented to the public shortly after CDC applied for its patents and years before the Patents-in-Suit issued. In February 2006, Dr. Heneine, a named inventor on the Patents-in-Suit, presented CDC's data at the Conference on Retroviruses and Opportunistic Infections (CROI) in Denver, Colorado.[54]

136. The results of the CDC's research were first published in the 2008 PLoS article.[55] The article reported that the CDC's findings "support PrEP trials for HIV prevention in humans and identified promising PrEP modalities."[56]

137. After the CDC's results were made public, they were received with excitement by the scientific community and received immediate media attention.[57] And the CDC research quickly increased interest in PrEP within the field.

138. For example, articles disclosing the patented regimens and the results of the inventors' research were nominated for the Charles C. Shepard Science Award, the premier CDC award for excellence in science.

139. In several instances, the prophylactic drug regimen in new or ongoing human clinical trials was changed from the administration of TDF alone to administration of TDF and FTC. These changes marked a major shift in researchers' thinking regarding which PrEP regimens

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[54] Walid Heneine, *Prevention of Rectal SHIV Transmission in Macaques by Tenofovir/FTC Combination*, 13TH CONFERENCE ON RETROVIRUSES AND OPPORTUNISTIC INFECTIONS (Feb. 5–8, 2006; Denver, Colo.), *conference report available at* http://www.natap.org/2006/CROI/CROI_23.htm [https://perma.cc/GYH4-45KA] (Exhibit 45).

[55] *See* García-Lerma et al., *supra* note 49.

[56] *Id*. at 291.

[57] *See, e.g.*, Marilynn Marchione, Associated Press, *AIDS Drugs Show Promise at Preventing Infection; Global Studies Expanded*, ASSOCIATED PRESS ARCHIVE (Mar. 27, 2006) (Exhibit 46), *syndicated at* ORANGE COUNTY REGISTER (Mar. 28, 2006, 3:00 AM), https://www.ocregister.com/2006/03/28/aids-drugs-show-prevention-promise/ [https://perma.cc/GES3-FHB6] (Exhibit 47).

would be most effective for prevention of HIV transmission in at-risk populations, and how effective those regimens would be.

140. For example, after CDC's findings were presented at CROI in 2006, two large PrEP trials switched from daily TDF to daily FTC/TDF, despite the delay and costs associated with such a change: the iPrEX (Pre-Exposure Prophylaxis Initiative) study and the Botswana FTC/TDF Oral HIV Prophylaxis Trial (TDF2) study.

141. These protocol changes (and their implications) were highlighted in many publications. For example, as stated in a 2006 Journal of American Medicine (JAMA) article, "Recent interest in PrEP as a prevention strategy has been based in part on encouraging preclinical data on combination PrEP and also on an announcement from the [CDC] [] about a switch in antiretroviral agent for the PrEP trial in Botswana from single agent tenofovir to combination emtricitabine/tenofovir (FTC/TDF). This attention appears to have created increased interest in PrEP . . . ."[58]

142. Even in the same issue as the García-Lerma 2008 *PLoS* article, an accompanying editorial described how CDC's groundbreaking research "will certainly affect the direction of human clinical trials and public health policy." It specifically concludes that "[t]hese results highlight an exciting and potentially important use of ART [antiretroviral therapy] to prevent sexual transmission of HIV, and offer further support for human clinical trials in progress or planned."[59]

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[58] *Effectiveness of Prevention Strategies*, *supra* note 23, at 863 (citations omitted).
[59] Myron S. Cohen & Angela D.M. Kashuba, *Antiretroviral Therapy for Prevention of HIV Infection: New Clues from an Animal Model*, 5 PLOS MED. (2) 190, 191 (2008), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2225431/ [https://perma.cc/JQK2-ARGS] (Exhibit 48).

143. PrEP studies since then have focused on the use of tenofovir prodrugs (including TDF) in combination with FTC, rather than single-drug regimens.

M. Numerous Subsequent Clinical Studies Confirming the Groundbreaking Efficacy of CDC's Inventive FTC/TDF Regimen

144. Today, a number of human studies have confirmed that an FTC/TDF PrEP regimen reduces the risk of getting HIV from sex by about 99 percent when taken daily by persons in high-risk populations.

145. Many of these studies were funded or otherwise supported by CDC, NIH, or other federal agencies. To date, the Government has spent hundreds of millions of dollars, much of it coming from the NIH and CDC, on clinical studies of FTC/tenofovir prodrug PrEP regimens, including Truvada for PrEP®.

146. While Gilead's public statements emphasize the amount of money it has spent to "support the clinical trials that led to the approval of Truvada for PrEP,"[60] that claim is disingenuous. Its support of early clinical trials was typically limited to only the donation of study drugs. Only after the commercial success of Truvada for PrEP® did Gilead increase its funding of PrEP clinical trials, and in particular, trials related to Descovy® for PrEP.

1. iPrEx Study

147. From 2007 to 2011, NIH sponsored a large scale study sponsored known as iPrEx. The study evaluated whether daily use of FTC and TDF could prevent HIV infection in 2,499 HIV-negative men and transgender women who were at high risk for HIV infections.

[60] *Gilead Statement, supra* note 44.

148. Results from iPrEx were published in the New England Journal of Medicine (NEJM) in late 2010.[61] This was the first published human study showing the clinical efficacy of PrEP. The results demonstrated that FTC/TDF was effective in reducing the risk of HIV infection by 44 percent compared with a placebo. With subjects who adhered to the FTC/TDF regimen, as demonstrated by detectable drug levels, the data showed that the odds of HIV infection were lowered by a factor of 12.9, with a relative reduction in HIV risk of 92 percent.[62]

149. The iPrEx results were met with wide acclaim. President Barack Obama placed a congratulatory phone call to NIH, and, in a formal statement, proclaimed that "these kinds of studies could mark the beginning of a new era in HIV prevention. As this research continues, the importance of using proven HIV prevention methods cannot be overstated."[63] Likewise, *TIME* magazine called the iPrEx results the most important "medical breakthrough" of 2010.[64]

150. Later analysis of the iPrEx data, which closely examined adherence to the regimen, showed that for participants who took seven FTC/TDF pills per week (a once-daily regimen), their estimated level of protection was 99 percent. For participants who took four FTC/TDF pills per week, their estimated level of protection was 96 percent. And for participants who took two

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[61] Robert M. Grant et al., *Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men*, 363 NEW ENG. J. MED. (27) 2587 (2010), *https://www.nejm.org/doi/full/10.1056/NEJMoa1011205* [https://perma.cc/FM3Z-9QLK] (Exhibit 49).

[62] *Id.* at 2596–97.

[63] *President Obama Welcomes New HIV Prevention Research Results*, THE WHITE HOUSE: OFFICE OF THE PRESS SECRETARY (Nov. 23, 2010), https://obamawhitehouse.archives.gov/the-press-office/2010/11/23/president-obama-welcomes-new-hiv-prevention-research-results [https://perma.cc/84N6-SGZN] (Exhibit 50).

[64] Alice Park, *The Top 10 Everything of 2010: Top 10 Medical Breakthroughs 1. AIDS Drugs Lower the Risk of HIV Infection*, TIME (Dec. 9, 2010), *available at* http://content.time.com/time/specials/packages/article/0,28804,2035319_2034529_2034513,00.html [https://perma.cc/7KDT-347X] (Exhibit 51).

FTC/TDF pills per week, their estimated level of protection was 76 percent.[65] Thus, the data established the efficacy of the once-daily regimen. It also validated the findings of CDC's original animal studies, which prompted the iPrEx protocol change to a dual-drug regimen.

151. In his testimony before the United States House Committee on Oversight and Reform (House Oversight Committee[66]) in May 2019, current Gilead CEO Daniel O'Day claimed that "we have two scientists . . . that were authors in the primary New England Journal article that is the study. And to be an author on the New England Journal . . . you must have involvement in the trial, in addition to the free medicine we provided and the know how."[67]

152. Mr. O'Day's statements are incorrect. Although two Gilead employees, Drs. James Rooney and Howard S. Jaffe, are identified as authors, the NEJM article characterizes Gilead's role in iPrEx as being non-substantive. The article states that "[t]he role of Gilead Sciences in the development of the protocol was limited to sections regarding the handling of the study drugs. *Neither Gilead Sciences nor any of its employees had a role in the accrual or analysis of the data or in the preparation of the manuscript*."[68]

153. On this point, the lead author of the NEJM article and leader of the iPrEx study, Dr. Robert Grant, Professor of Medicine at the University of California, San Francisco, testified to the

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[65] *See* San Francisco AIDS Foundation, *The Basics*, PREPFACTS.ORG, https://prepfacts.org/prep/the-basics/ [https://perma.cc/6BKW-W444] (Exhibit 52) (citing Peter L. Anderson et al., *Emtricitabine-Tenofovir Concentrations and Pre-Exposure Prophylaxis Efficacy in Men Who Have Sex with Men*, 4 SCI. TRANSLATIONAL MED. (151ra125), 1 (2012), *available at* https://stm.sciencemag.org/content/4/151/151ra125 [https://perma.cc/BYT8-C2RC] (Exhibit 53)).

[66] The House Oversight Committee is the principal investigative committee of the U.S. House of Representatives.

[67] *H. Comm. Hearing*, *supra* note 51, at 21 (statement of Mr. Daniel O'Day, Chairman and CEO, Gilead Sciences, Inc.); Bloomberg Transcript, *supra* note 51, at 27.

[68] Grant et al., *supra* note 61, at 2589 (emphasis added).

House Oversight Committee that Gilead has been "a hesitant partner on PrEP research," noting that it "did not provide leadership, innovation, or funding for PrEP research," but rather limited itself "to donating study drug and placebos."[69]

154. The bulk of iPrEx funding came from a grant from the National Institute of Allergy and Infectious Diseases (NIAID), roughly $50 million in total. An additional $17 million of funding was provided by the Bill and Melinda Gates Foundation (Gates Foundation). Gilead provided FTC, TDF, tenofovir and other medication used in iPrEx, but no monetary funding.[70]

2. Partners PrEP Study

155. Initiated in 2007, the Partners PrEP study enrolled over 4,700 heterosexual couples where one partner was HIV-positive and the other was not. The study evaluated the efficacy and safety of the combination of FTC/TDF present in Truvada® and TDF-alone in preventing HIV infection in the HIV-negative partner.[71]

156. Results published in 2012 showed the combination of FTC/TDF present in Truvada® reduced the risk of becoming infected compared with placebo in an amount consistent with the CDC animal data on which the Patents-in-Suit were filed. As with iPrEx, efficacy among Partners PrEP participants was strongly correlated with drug regimen adherence.[72]

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[69] *H. Comm. Hearing*, *supra* note 51, at 5.
[70] *See* Grant et al., *supra* note 61, at 2598.
[71] Jared M. Baeten et al., *Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women*, 367 NEW ENG. J. MED. (5) 399 (2012), https://www.nejm.org/doi/full/10.1056/NEJMoa1108524 [https://perma.cc/V3Q9-7K97] (Exhibit 54).
[72] *Id*. at 407–408 ("Adherence to preexposure prophylaxis, protection against HIV-1 infection, and antiretroviral resistance appear to be tightly interwoven.").

157. Where adherence could be confirmed by measuring detectable drugs, the FTC/TDF regimen had an efficacy of 93 percent.[73]

158. Partners PrEP was funded by a $70 million grant from the Gates Foundation along with some NIH funding for HIV-1 testing.[74] Additional assistance was provided from a number of CDC investigators, clinicians, and facilities. Many of these CDC resources werein Africa, where the trials took place. But like the iPrEx study, Gilead provided only study medication, and again no funding.[75]

159. Unlike the iPrEx study, no Gilead personnel were named as co-authors when the Partners PrEP results were published in the NEJM.[76]

3. TDF2 Study

160. The TDF2 study was funded by CDC and NIH, and was the second study to change its protocol from TDF-only to FTC/TDF after CDC's patented research became public.[77]

161. Published in 2012, the TDF2 study examined the use of once-daily Truvada® pills as an HIV PrEP regimen in over 1,200 heterosexual men and women in Botswana, which at the

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[73] Jared M. Baeten et al., *Single-Agent Tenofovir Versus Combination Emtricitabine/Tenofovir for Pre-Exposure Prophylaxis for HIV-1 Acquisition: A Randomized Trial*, 14 LANCET INFECTIOUS DISEASES (11) 1055 (2014), *republished at* National Institute of Health Public Access, Nov. 1, 2015, at 2, 8, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4252589/ [https://perma.cc/NVS3-2WMN] (Exhibit 55).

[74] *Id*. at 1064 (PDF p. 11) ("Central laboratory support for HIV-1 testing was provided in part through the University of Washington Center for AIDS Research, funded by the US National Institutes of Health (award number P30 AI027757)").

[75] Baeten et al., *supra* note 71, at 400 ("Gilead Sciences donated the study medication but had no role in data collection data analysis, or manuscript preparation."); *id.* at 409 ("We thank . . . Dr. James Rooney and others at Gilead Sciences for donating the study drug.").

[76] *Id*. at 399, 409.

[77] *See* Michael C. Thigpen et al., *Antiretroviral Preexposure Prophylaxis for Heterosexual HIV Transmission in Botswana*, 367 NEW ENGL. J. MED. 423, 424 (2012), https://www.nejm.org/doi/full/10.1056/NEJMoa1110711 [https://perma.cc/8TCU-RSPR] (Exhibit 56) ("When data from studies in animals later showed the superior efficacy of TDF–FTC, we changed the active drug to TDF–FTC (TDF2 study).").

time had the world's second highest prevalence of HIV infection. The study found that "[d]aily TDF–FTC prophylaxis prevented HIV infection in sexually active heterosexual adults," particularly where adherence to the regimen could be established.[78]

162. Although the study did not confirm adherence by measuring detectable drug in the subjects' bloodstream, the daily FTC/TDF regimen protected 62.2 percent of adhering and non-adhering study subjects from HIV infections. When data were excluded for subjects tested more than 30 days after their last reported dose of study medication, the study showed an efficacy of 77.9 percent.

4. PROUD Study

163. Later studies (occurring after Truvada for PrEP® was commercially established) found a daily FTC/TDF regimen to have even higher levels of efficacy in real-world settings, where stricter adherence to the drug regimen was confirmed.

164. The PROUD study, sponsored by public health organizations in the United Kingdom, evaluated daily FTC/TDF regimens in men who have sex with men and who were at high risk for HIV infection.[79] The PROUD researchers also received some support from Gilead, which "provided Truvada, distributed drug to clinics, and awarded a grant for the additional diagnostic tests including drug concentrations in plasma."[80]

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[78] *Id*. at 433.
[79] *See* Sheena McCormack et al., *Pre-exposure Prophylaxis to Prevent the Acquisition of HIV-1 Infection (PROUD): Effectiveness Results from the Pilot Phase of a Pragmatic Open-Label Randomised Trial*, 387 THE LANCET 53 (2016), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4700047/ [https://perma.cc/3G8N-MVQA] (Exhibit 57).
[80] *Id.* at 59.

165. In 2015, the PROUD researchers presented their findings that daily PrEP had protected 86 percent of its subjects from infection,[81] which correlated to almost 100 percent clinical efficacy when adherence was confirmed by detectable drugs in the bloodstream.[82]

5. ANRS-IPERGAY Study

166. Around the same time as PROUD, researchers announced similar results for French and Canadian men who have sex with men in the IPERGAY Study, funded by the French National Agency for Research on AIDS (ANRS) and other entities.[83] "Gilead Sciences donated the study medications and provided funding for the pharmacokinetics analysis but had no role in data collection, data analysis, or manuscript preparation."[84]

167. Rather than a daily regimen, as in previous PrEP studies, participants in the IPERGAY study were administered FTC and TDF "on demand," taking two doses of medication 2-24 hours before sex and two additional single doses 24 and 48 hours after the last pre-sex dose.[85] Similar to the PROUD study, the ANRS-IPERGAY study showed that "on demand" PrEP had

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[81] Sheena McCormack & David Dunn, Infections Group, MRC Clinical Trials Unit, Univ. College of London, *Pragmatic Open-Label Randomised Trial of Preexposure Prophylaxis: The PROUD Study*, 22ND CONFERENCE ON RETROVIRUSES AND OPPORTUNISTIC INFECTIONS (Feb. 23–26, 2015; Seattle, Wash.), *conference abstract available at* http://www.croiconference.org/sessions/pragmatic-open-label-randomised-trial-preexposure-prophylaxis-proud-study [https://perma.cc/X83H-82RL] (Exhibit 58); *see also PROUD Study Shows Pre-Exposure Prophylaxis is Highly Protective Against HIV Infection*, MRC CLINICAL TRIALS UNIT AT UNIVERSITY COLLEGE LONDON (Feb. 24, 2015), http://www.proud.mrc.ac.uk/media/1102/proud_press_release.pdf [https://perma.cc/R9QS-EFJC] (Exhibit 59).

[82] *See* McCormack et al., *supra* note 79, at 57 ("These findings suggest that there were no breakthrough HIV infections in participants who were taking PrEP.").

[83] Jean-Michael Molina et al., *On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection*, 373 NEW ENG. J. MED. (23) 2237 (2015), https://www.nejm.org/doi/full/10.1056/NEJMoa1506273 [https://perma.cc/43XR-CWBB] (Exhibit 60).

[84] *Id.* at 2239; *see also id*. at 2245 ("Gilead Sciences donated the TDF-FTC and placebo used in the study and funding for the pharmacokinetics analysis.").

[85] *Id.* at 2238.

protected 86 percent of its subjects from infection,[86] and the open-label extension of the study showed an about 97 percent relative reduction of HIV incidence as compared with the placebo group of the double-blind phase.[87]

6. CDC's Methodology Now "Gold Standard" For Clinical Researchers

168. In view of all the data now available from FTC/TDF studies, the animal studies that underlie CDC's patented research accurately predicted the high efficacy of PrEP seen in later human trials.

169. Based on the accuracy of its macaque modeling, CDC's methodology and study design have become the "gold standard" for clinical researchers in testing new PrEP regimens. And collecting such data is now considered critical to any researcher seeking to pursue human trials.

N. Approval and Sales of Truvada® and Quick Approval of Descovy® That Followed from CDC's Inventive Work

170. In July 2012, FDA approved Truvada® for use as PrEP (trademarked by Gilead as Truvada for PrEP®). This approval and the eventual massive sales of Truvada® can be traced back to CDC's patented research.

171. The switch among clinicians to an FTC/TDF regimen in clinical studies after publication of CDC's data provided the clinical support that led to FDA approval of Truvada for PrEP®. In particular, Gilead's FDA application relied principally on the clinical evidence in the iPrEx and Partners PrEP studies that the drug was safe and effective at preventing HIV

[86] *Id*. at 2244.
[87] Jean-Michel Molina et al., *Efficacy, Safety, and Effect on Sexual Behaviour of On-Demand Pre-Exposure Prophylaxis for HIV in Men Who Have Sex with Men: An Observational Cohort Study*, 4 LANCET HIV (9) e402, e407 (2017), https://www.ncbi.nlm.nih.gov/pubmed/28747274 [https://perma.cc/JH5G-AVE4] (Exhibit 61).

transmission in populations at increased risk of infection. Other than donating drugs, Gilead did not support any of the clinical efforts leading to FDA approval, and indeed openly expressed skepticism regarding PrEP.[88]

172. Even after Truvada® was approved for use as PrEP, Gilead was initially reluctant to promote and support PrEP commercially. It did develop and support educational initiatives and demonstration projects designed to identify at-risk persons who could benefit from PrEP, but did not widely market PrEP or sponsor any clinical studies in the years immediately following FDA approval.

173. In a September 2013 article in *The New Yorker*, Dr. James Rooney, Gilead's Vice President of Medical Affairs, stated that Gilead, despite spending "several million dollars" on PrEP initiatives, did not "view PrEP as a commercial opportunity." Dr. Rooney explained that "[t]he role of antiretrovirals in H.I.V. prevention is not yet defined and not yet broadly accepted."[89]

174. The article further noted that existing global Truvada® sales for the treatment of HIV infection totaled over $3 billion in 2012.[90] At that time, the cost of Truvada® was approximately $15,000 per year (or $1,250 per month) in the United States.[91]

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[88] *See* Jon Cohen, *Anti-HIV Pill Protects Against AIDS*, SCIENCE, Nov. 23, 2010, https://www.sciencemag.org/news/2010/11/anti-hiv-pill-protects-against-aids [https://perma.cc/4T5C-W4CH] (Exhibit 62) ("Gilead says it wants to have 'frank' talks with the U.S. Food and Drug Administration and other stakeholders before it decides to seek licensure for Truvada as a preventive. 'We'll have, I imagine, a very interesting discussion about the potential risks and benefits associated with this kind of a modality, and I think that will govern what we choose to do,' says Howard Jaffe, president of the Gilead Foundation.").

[89] Christopher Glazek, *Why Is No One on The First Treatment to Prevent H.I.V.?*, THE NEW YORKER: ANNALS OF TECHNOLOGY, Sept. 13, 2013, https://www.newyorker.com/tech/annals-of-technology/why-is-no-one-on-the-first-treatment-to-prevent-h-i-v [https://perma.cc/9KS5-8FVS] (Exhibit 63).

[90] *Id.*

[91] Barry Coutinho & Ramakrishna Prasad, *Emtricitabine/Tenofovir (Truvada) for HIV Prophylaxis*, 88 American Family Physician (8) 539 (2013),

175. In 2014, based on favorable clinical data that mirrored the initial CDC animal results, CDC issued comprehensive clinical guidelines recommending that daily PrEP be considered for HIV prevention in all people who are at substantial risk. The World Health Organization (WHO) issued a similar recommendation in 2015 after studies showed that PrEP was highly effective at reducing the risk of HIV infection among high-risk populations in real-world settings.[92]

176. Following the new guidelines, sales for Truvada for PrEP® skyrocketed, both in the United States and worldwide. In 2016, there were 77,120 PrEP users in the United States, as compared to 8,768 PrEP users in 2012.[93]

177. In recent years, PrEP use has continued to expand. In 2018, there were over 200,000 PrEP users in the United States. But that number is still far less than the 1.1 million American adults at high risk of HIV infection who CDC estimates could benefit from PrEP.

178. In response to the increased demand for Truvada for PrEP®, Gilead has significantly increased the price it charges for this drug. Presently, Truvada for PrEP® sells for about $1,800

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https://www.aafp.org/afp/2013/1015/p535.html#afp20131015p535-b7 [https://perma.cc/9VZG-SQNF] (Exhibit 64).

[92] *Policy Brief: WHO Expands Recommendation on Oral Preexposure Prophylaxis of HIV Infection (PrEP)*,WORLD HEALTH ORGANIZATION (Nov. 2015), https://apps.who.int/iris/bitstream/handle/10665/197906/WHO_HIV_2015.48_eng.pdf;jsessionid=0EED25F90C1914C313B7C06916AAC0F0?sequence=1 [https://perma.cc/N5XB-4NFJ] (Exhibit 65).

[93] *Mapping PrEP: First Ever Data on PrEP Users Across the U.S.*, AIDSVU, https://aidsvu.org/prep [https://perma.cc/2P56-C34H] (Exhibit 66); *see also* AIDSVu graphic, https://aidsvu.org/wp-content/uploads/2018/03/2-AIDSVu-PrEP_77000-Graphic-1024-x-512-v10.png [https://perma.cc/2YZJ-XLK5] (Exhibit 67).

per month in the United States.[94] Those sales account for much of the $3 billion that Gilead earned from Truvada® last year.

179. With its U.S. patents for Truvada® expiring in 2021, Gilead has sought in recent years to obtain FDA approval for its antiretroviral drug Descovy® for use as PrEP.

180. On August 7, 2019, an FDA advisory committee recommended approval of Descovy® for PrEP to reduce the risk of sexually acquired HIV-1 infection in men and transgender women who have sex with men.

181. Following these recommendations, FDA approved Descovy for PrEP on October 3, 2019 for those groups, but did not approve Descovy® for PrEP for many women, namely those "at risk of HIV-1 from receptive vaginal sex because the effectiveness in this population has not been evaluated."[95]

O. PrEP as Critical Component of Effort to End HIV Epidemic

182. Today, PrEP is a critical component of the Government's efforts to end the HIV epidemic. During the 2019 State of the Union address, President Donald J. Trump announced a new initiative entitled "Ending the HIV Epidemic: A Plan for America," with the goal of reducing

[94] Shefali Luthra & Anna Gorman, *Rising Cost of PrEP to Prevent HIV Infection Pushes It out of Reach for Many*, NPR (June 30, 2018), https://www.npr.org/sections/health-shots/2018/06/30/624045995/rising-cost-of-prep-a-pill-that-prevents-hiv-pushes-it-out-of-reach-for-many [https://perma.cc/KL8C-392M] (Exhibit 68) ("Since brand-name Truvada was approved for HIV prevention six years ago, its average wholesale price has increased by about 45 percent. Now, the drug — which rakes in billions of dollars in annual global revenue for its manufacturer, Gilead Sciences — carries a list price of close to $2,000 for a 30-day supply."); *see also* Fitzsimons, *infra* note 103, at 4 ("While a month's supply of generic Truvada is available in countries around the world for as little as $70, in the United States a month's supply sells for $1,600 to $2,000[.]"). As of March 2019, the wholesale acquisition cost (WAC) of a month supply of Truvada was $1757.90.

[95] *FDA Approves Second Drug to Prevent HIV*, *supra* note 5.

new HIV infections by 90 percent by 2030.[96] CDC's efforts in this regard will put particular focus on working closely with other HHS agencies, local and state governments, communities, and people with HIV to expand new HIV prevention and treatment efforts in 48 counties with the highest HIV burden; Washington, D.C.; San Juan, Puerto Rico; and seven states with disproportionate rural burdens.[97]

183. CDC's efforts will focus on four key strategies that together can end the HIV epidemic in the U.S.: 1) diagnose all people with HIV as early as possible; 2) treat HIV rapidly and effectively after diagnosis in all people with HIV to help them get and stay virally suppressed; 3) prevent HIV transmissions using proven prevention interventions, including PrEP and syringe service programs; and 4) respond quickly to potential HIV outbreaks to get prevention and treatment services to people who need them.[98]

184. Administration of (and access to) Truvada for PrEP® will be a key focal point for prevention efforts in the identified geographic areas, or "hot spots," across the United States.

185. One barrier to these efforts is the stigma sometimes associated with PrEP users and other challenges related to reaching marginalized and hard-to-reach communities at high risk for HIV infection.

186. Another critical barrier to increasing access to PrEP in the United States has been the cost of Truvada®, which presently is only sold by Gilead, by virtue of U.S. patents that

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[96] *See What is 'Ending the HIV Epidemic: A Plan for America'?*, HIV.GOV, https://www.hiv.gov/federal-response/ending-the-hiv-epidemic/overview, [https://perma.cc/32YQ-A66N] (last updated Sept. 3, 2019) (Exhibit 69).
[97] *Id.*; *see also Ending the HIV Epidemic Counties, Territories and States*, HIV.GOV, https://files.hiv.gov/s3fs-public/Ending-the-HIV-Epidemic-Counties-and-Territories.pdf, [https://perma.cc/V27J-ZC4Q] (updated Feb. 7, 2019) (Exhibit 70).
[98] *Supra* note 96 (PDF p. 7).

purportedly cover the product. This is a major reason that many at risk of HIV infection in the United States are not currently taking Truvada for PrEP®.

187. Many AIDS activists and many in the medical community have criticized Truvada®'s price in the United States, particularly in light of HHS's patents, the Government's funding of clinical research on PrEP, and the relatively low cost at which Gilead apparently makes the product.[99] This criticism was the principal focus of a House Oversight Committee hearing held in May 2019. [100]

188. On the issue of cost and access, many advocates and activists also point to PrEP use in Australia, where its government-funded roll-out of free Truvada for PrEP® in New South Wales reduced new HIV diagnoses by 25 percent in the one year of research, the lowest rate in that state since 1985.[101]

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[99] #BreakThePatent, https://breakthepatent.org [https://perma.cc/8FT5-Q7UV] (Exhibit 71) ("The drug costs less than $6 a month to make but Gilead charges patients more than $1,600 for a 30 day supply."); *id*. ("The manufacturer of the Truvada, Gilead Sciences, has inflated the price by more than 25,000% . . . [w]hat Gilead charges for just two pills could pay for an entire year's supply of a generic equivalent.").

[100] See H. Comm. Hearing, *supra* note 51 ("HIV PREVENTION DRUG: BILLIONS IN CORPORATE PROFITS AFTER MILLIONS IN TAXPAYER INVESTMENTS"); *see also id.* at 2 (statement of Chairman Elijah Cummings) ("When Truvada was first approved in 2004, Gilead charged about $800 per month, again, for this lifesaving drug. Since then, Gilead raised the price of this drug over and over and over and over and over again. It now charges about $2,000 for just one month or about $70 per pill. . . . how can our system let a company charge prices that are so outrageous, making $36 billion while there are literally hundreds of thousands of people who need this drug?").

[101] *See, e.g.*, Nina Avramova, *PrEP Can 'Significantly' Reduce HIV Rates Across Populations, Study Says*, CNN (Oct. 17, 2018, 3:00 PM ET), https://www.cnn.com/2018/10/17/health/hiv-reduction-men-prep-australia-intl-study/index.html [https://perma.cc/S5KN-PE7U] (Exhibit 72) ("Based on introduction of the intervention, HIV infections diagnosed in men who have sex with men in the Australian state of New South Wales fell by a quarter -- 25.1% -- in one year in the research, published Wednesday in the journal the Lancet."); *see also* Sheena McCormack, *What Happens When PrEP is Scaled up? Results from EPIC-NSW*, 5 The Lancet HIV (11) e607, e607-08 (Oct. 17, 2018), https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(18)30253-4/fulltext [https://perma.cc/SKG2-T2EQ] (Exhibit 73).

P. Teva Settlement Announcement

189. In response to criticism of its pricing, Gilead has taken a number of public actions to address this issue.

190. For example, on May 8, 2019, nine days prior to the House Oversight Committee hearing, Gilead announced a settlement that would permit marketing in the United States of a generic equivalent of the Truvada for PrEP® product from Teva Pharmaceuticals Industries Ltd. (Teva) on September 30, 2020, roughly one year ahead of the expiration of its Truvada®-related patents.[102]

191. According to an email sent the same day (May 8) to investors by Douglas M. Brooks, Gilead's Executive Director for Community Engagement, the parties agreed to the September 2020 date under a patent-related settlement reached in 2014. Mr. Brooks' email also denied that this settlement was "related to current discussions with the U.S. government to broaden access to Truvada for PrEP[®] for vulnerable populations and support the federal plan to end the HIV epidemic."[103]

192. Based on information and belief, no terms of the Gilead-Teva settlement have ever been publicly disclosed.

193. AIDS activists questioned the settlement's impact on access to Truvada for PrEP®. For example, Dr. Aaron Lord, a PrEP user and a founder of the PrEP4All Collaboration advocacy

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[102] *See* Gilead Sciences, Inc., Quarterly Report (Form 10-Q), at 35 (May 8, 2019), http://investors.gilead.com/static-files/0ff8d741-b9eb-4162-bcb4-f16094d37254 [https://perma.cc/QG3P-VJXE] (Exhibit 74) ("Pursuant to a settlement agreement relating to patents that protect Truvada and Atripla, Teva Pharmaceuticals will be able to launch generic fixed-dose combinations of emtricitabine and TDF and generic fixed-dose combinations of emtricitabine, TDF and efavirenz in the United States on September 30, 2020.").

[103] Tim Fitzsimons, *Generic HIV Prevention Drug Coming in 2020, Gilead Says*, NBC NEWS (May 8, 2019, 1:53 PM EDT), https://www.cnbc.com/2019/05/08/generic-hiv-prevention-drug-coming-in-2020-gilead-says.html [https://perma.cc/3Y5E-WWJQ] (Exhibit 75).

group, stated that the settlement "leaves Gilead with exclusive rights to Truvada as PrEP for another 15 months and Teva as the only generic manufacturer on the U.S. market. This will do little to reduce the price in a way that will increase access and PrEP4All remains suspicious of the terms and lack of transparency surrounding the Teva settlement."[104]

194. Similarly, Mr. Horn, on behalf of NASTAD (the National Alliance of State and Territorial AIDS Directors), also questioned the impact of the Teva settlement on pricing, stating: "Historically, when there's only one generic manufacturer in the field, the price difference is a miniscule 10% to 15%. The real savings for all purchasers and payers won't begin until there's robust generic competition."[105]

195. The launch of Teva's soon-to-be generic product is being preceded by Gilead's current launch of Descovy® for PrEP. This presumably will decrease sales of Truvada® and generic equivalents in the PrEP market. And patient assistance programs Gilead currently offers for Truvada for PrEP® users may also affect the willingness of users to convert to a generic equivalent.

V. CDC'S PATENTS

196. At issue here are four Government-owned patents resulting from CDC's research on FTC/tenofovir and FTC/tenofovir prodrug regimens for PrEP. The claims of these patents generally cover processes for protecting a primate or human host from a self-replicating infection by an immunodeficiency retrovirus, including HIV. In the claimed inventions, the protection is

[104] Aaron S. Lord, MD, *Official Statement Responding to Gilead Sciences' Announcement That it Will Allow Teva to Manufacture a Generic Version of Truvada*, #BreakThePatent (May 8, 2019), https://breakthepatent.org/official-statement-responding-to-gilead-sciences-announcement-that-it-will-be-release-its-patent-on-truvada-a-year-early [https://perma.cc/9PR3-L8US] (Exhibit 76).
[105] Trenton Straube, *Generic PrEP To Arrive In September 2020, But Will Big Savings Follow?*, POZ MAGAZINE (May 9, 2019), https://www.poz.com/article/generic-prep-arrive-september-2020-will-big-savings-follow [https://perma.cc/6C6V-TMDQ] (Exhibit 77).

provided by a combination of a nucleoside reverse transcriptase inhibitor, such as FTC, and a nucleotide reverse transcriptase inhibitor, such as tenofovir, or esters/prodrugs of tenofovir, such as TDF or TAF.

A. The '509 Patent

197. The '509 patent (Exhibit 1) is entitled "Inhibition of HIV Infection through Chemoprophylaxis," and issued on June 2, 2015. It claims priority to the 2006 Provisional Application.

198. The '509 patent lists five current or former CDC scientists as inventors: Drs. Walid Heneine, Thomas M. Folks, Robert Janssen, Ronald Otten, and Jose Gerardo García-Lerma (collectively, the Inventors).

199. The '509 patent is assigned to the United States of America, as represented by the Secretary of HHS, as the result of written assignments from the Inventors prior to issuance.

200. The '509 patent features two independent claims: claims 1 and 12.

Claim 1 recites:

> 1. A process of protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus comprising:
>
> (a) selecting a primate host not infected with the immunodeficiency retrovirus, and
>
> (b) administering directly to an uninfected primate host a combination comprising:
>
> i. a pharmaceutically effective amount of emtricitabine; and
>
> ii. a pharmaceutically effective amount of tenofovir or tenofovir disoproxil fumarate,
>
> wherein the combination is administered prior to an exposure of the primate host to the immunodeficiency retrovirus, thereby protecting the primate host from infection with the immunodeficiency retrovirus, wherein the combination is administered orally.

201. Claim 12 recites a similar process, except for being directed to "[a] process for inhibiting [the] establishment of a self-replicating infection of human immunodeficiency virus in a human," rather than a primate:

12. A process for inhibiting establishment of a human immunodeficiency virus self-replicating infection of human immunodeficiency virus infection in a human, comprising:

(a) selecting an uninfected human that does not have the self-replicating infection; and

(b) administering to the uninfected human a combination comprising:

i. a pharmaceutically effective amount of emtricitabine; and

ii. a pharmaceutically effective amount of tenofovir or tenofovir ester;

thereby inhibiting the establishment of the self-replicating infection with the immunodeficiency virus in the human, wherein the combination is administered orally.

202. TDF and TAF are both tenofovir esters.

203. Claim 13 depends from Claim 12 and recites: "The process of claim **12** wherein the combination is administered *prior to a potential exposure* of the primate host to the human immunodeficiency retrovirus." (second emphasis added).

204. The '509 patent will expire on May 12, 2031.

205. Since the issuance of the '509 patent, the Government has acquired three additional patents based on the same disclosure of the '509 patent.

B. <u>The '333 Patent</u>

206. The '333 patent (Exhibit 2) issued on February 28, 2017.

207. The '333 patent is assigned to the United States of America, as represented by the Secretary of HHS, as the result of written assignments from the Inventors prior to issuance.

208. The '333 patent contains two independent claims: claims 1 and 12.

209. Claim 1 recites:

1. A process of protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus comprising:

(a) selecting a primate host not infected with the immunodeficiency retrovirus, and

(b) administering directly to an uninfected primate host a combination comprising:

i. a pharmaceutically effective amount of emtricitabine, wherein the pharmaceutically effective amount of the emtricitabine is administered orally, subcutaneously or vaginally; and

ii. a pharmaceutically effective amount of tenofovir or tenofovir disoproxil fumarate, wherein the pharmaceutically effective amount of the tenofovir or tenofovir disoproxil fumarate is administered orally, subcutaneously or vaginally,

and wherein the combination is administered prior to the exposure of the primate host to the immunodeficiency retrovirus, thereby protecting the primate host from infection with the immunodeficiency retrovirus.

210. Claim 12 recites:

12. A process for inhibiting establishment of a human immunodeficiency virus self-replicating infection of human immunodeficiency virus infection in a human, comprising:

(a) selecting an uninfected human that does not have the self-replicating infection; and

(b) administering to the uninfected human a combination comprising:

i. a pharmaceutically effective amount of emtricitabine wherein the pharmaceutically effective amount of the emtricitabine is administered orally, subcutaneously or vaginally; and

ii. a pharmaceutically effective amount of tenofovir or tenofovir disoproxil fumarate wherein the pharmaceutically effective amount of the tenofovir or tenofovir disoproxil fumarate is administered orally, subcutaneously or vaginally;

thereby inhibiting the establishment of the self-replicating infection with the immunodeficiency virus in the human.

211. Claim 13 depends from Claim 12 and recites: "The process of claim **12** wherein the combination is administered *prior to a potential exposure* of the human to the human immunodeficiency retrovirus." (second emphasis added).

C. The '191 Patent

212. The '191 patent (Exhibit 3) issued on April 10, 2018.

213. The '191 patent is assigned to the United States of America, as represented by the Secretary of HHS, as the result of written assignments from the Inventors prior to issuance.

214. The '191 patent contains two independent claims: claims 1 and 13.

215. Claim 1 recites:

1. A process of protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus comprising:

(a) selecting a primate host not infected with the immunodeficiency retrovirus, and

(b) administering directly to an uninfected primate host a combination comprising:

i. a pharmaceutically effective amount of emtricitabine; and

ii. a pharmaceutically effective amount of tenofovir or tenofovir disoproxil fumarate,

wherein the combination is administered orally in tablet form prior to the exposure of the primate host to the immunodeficiency retrovirus,

thereby protecting the primate host from infection with the immunodeficiency retrovirus.

216. Claim 13 recites:

13. A process for inhibiting establishment of a human immunodeficiency virus self-replicating infection of human immunodeficiency virus infection in a human, comprising:

(a) selecting an uninfected human that does not have the self-replicating infection; and

(b) administering to the uninfected human a combination comprising:

i. a pharmaceutically effective amount of emtricitabine in a tablet; and

ii. a pharmaceutically effective amount of tenofovir or a tenofovir disoproxil fumerate in a tablet;

thereby inhibiting the establishment of the self-replicating infection with the immunodeficiency virus in the human, wherein the combination is administered prior to a potential exposure of the human to the human immunodeficiency retrovirus.

D. <u>The ’423 Patent</u>

217. The ’423 patent (Exhibit 4) issued on July 2, 2019.

218. The ’509 patent is assigned to the United States of America, as represented by the Secretary of HHS, as the result of written assignments from the Inventors prior to issuance.

219. The ’423 patent contains two independent claims: Claims 1 and 12.

220. Claim 1 recites:

1. A process of protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus comprising:

(a) selecting a primate host not infected with the immunodeficiency retrovirus, and

(b) administering directly to the primate host a combination comprising:

i. a pharmaceutically effective amount of emtricitabine; and

ii. a pharmaceutically effective amount of tenofovir or a tenofovir prodrug,

wherein the combination is administered orally prior to the exposure of the primate host to the immunodeficiency retrovirus,
thereby protecting the primate host from infection with the immunodeficiency retrovirus.

221. Claim 12 recites:

12. A process for inhibiting establishment of a human immunodeficiency virus self-replicating infection of human immunodeficiency vims infection in a human, comprising:
(a) selecting an uninfected human that does not have the self-replicating infection; and
(b) administering to the uninfected human a combination comprising:
i. a pharmaceutically effective amount of emtricitabine; and
ii. a pharmaceutically effective amount of tenofovir or a tenofovir prodrug;
thereby inhibiting the establishment of the self-replicating infection with the immunodeficiency virus in the human, wherein the combination is administered prior to potential exposure the human to the human immunodeficiency retrovirus.

222. TDF and TAF are both tenofovir prodrugs.

223. As a result of terminal disclaimers, the ’333, ’191, and ’423 patents expire on January 31, 2027. All three also share the same title and list the same inventors as the ’509 patent.

VI. CDC’S EFFORTS TO LICENSE THE PATENTS-IN-SUIT

A. CDC’s Licensing of Its Patented Work Outside the United States

224. Gilead has patents that prevent the sale by others of pharmaceutical combinations of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) (Truvada®) in the United States, but generic equivalents to Truvada® are now on the market in many other countries.

225. Of the companies with approval, or seeking approval, to market generic equivalents to Truvada® abroad, the only company to acquire a multi-country license to the patent rights at issue is Mylan, N.V. (Mylan), which is currently selling its generic Truvada® product in Australia, Canada, Germany, France, and the United Kingdom, where HHS owns foreign counterparts to the Patents-in-Suit.

226. Before taking a license, Mylan challenged CDC's European Patent No. 2,015,753, a foreign counterpart to the Patents-in-Suit, in a multi-year proceeding before the European Patent Office known as an opposition.

227. The claims of CDC's European patent were upheld as valid.

228. Mylan subsequently entered into a settlement agreement in 2016 with CDC, which included a worldwide non-exclusive license to the rights to the Patents-in-Suit and related foreign patents.

229. Mylan has agreed to pay royalties for products sold or manufactured in Australia, Canada, Germany, France, and the United Kingdom.

230. Additionally, TAD Pharma GmbH has taken a license to the patented technology to sell a generic equivalent to Truvada for PrEP® in Germany.

231. Additionally, the Technology Transfer and Intellectual Property Office of NIAID (NIAID/TTIPO), which has responsibility for patenting and licensing CDC inventions, is actively negotiating with other companies seeking to sell a generic equivalent to Truvada® in Europe, Australia, and/or Canada. NIAID/TTIPO also continues to seek license agreements with other companies already selling generic equivalents to Truvada® in Europe, Australia, and/or Canada.

232. Gilead, however, has continued to sell Truvada for PrEP® worldwide without paying any royalties to CDC.

B. Gilead's Refusal to Take a License to CDC's Patents

233. Even before issuance of the '509 patent, the NIH Office of Technology Transfer (NIH/OTT) and NIAID/TTIPO contacted Gilead officials regarding the patented technology.

234. In October 2014, NIH/OTT emailed both Dr. Jay Parrish, then a member of Gilead's Corporate Development Team, and Dr. Linda Higgins, Gilead's Vice-President of Biology, giving them notice of CDC's patented technology.

235. The notice stated that the CDC researchers had shown that "daily pre-exposure prophylaxis (PrEP) with emtricitabine in combination with tenofovir disoproxil fumarate (Truvada) significantly increases the level of protection against HIV transmission" and that "[t]he CDC is pursuing U.S. and foreign patent protection for this technology."[106]

236. NIH/OTT received no response to the emailed notice.

237. By October 2015, CDC patenting and licensing authority moved within NIH from NIH/OTT to NIAID/TTIPO.

238. Beginning in March 2016, after issuance of the '509 patent in 2015, NIAID/TTIPO began to repeatedly invite Gilead to take a worldwide license to these patent rights (including rights to all of the eventual Patents-in-Suit). The initial email communication included a copy of the '509 patent, a list of related patent applications (U.S. and foreign), and a standard license application form.

239. Gilead officials did not immediately respond to this communication, and ultimately directed NIAID/TTIPO to Gilead's outside counsel at WilmerHale LLP in April 2016. After communications with attorneys at that firm, NIAID/TTIPO received no response from Gilead.

240. Nonetheless, NIAID/TTIPO and CDC continued their efforts to resolve this dispute without litigation. After NIAID/TTIPO reestablished contact with Gilead in January 2017, the parties engaged in two confidential conferences later in 2017, and continued to correspond and communicate in 2018, but were unable to resolve the dispute and enter into a license agreement.

241. Gilead has never denied that it infringes CDC's patents. Nonetheless, by 2019, it became clear that Gilead would not take a license to the Patents-in-Suit on any reasonable terms.

[106] Email from NIH/OTT to Dr. Parrish, Gilead Sciences, Inc. (Oct. 23, 2014, 11:39 AM) (Exhibit 78).

Instead, as demonstrated by the testimony of Gilead's CEO Daniel O'Day before the House Oversight Committee in May 2019, Gilead has publicly and repeatedly stated its position that the Patents-in-Suit are invalid.

242. In his testimony, Mr. O'Day stated that "[u]sing Truvada for PrEP was well known in the scientific community, long before CDC claimed it as an invention," but despite this position, Gilead has "chosen not to challenge those patents because we value our collaborative relationship with the agency."[107]

243. In an about-face, just three months after Mr. O'Day's statement, Gilead challenged the validity of all four Patents-in-Suit by petitioning for *inter partes* review (IPR) at the PTO. Gilead filed petitions on August 21, 2019, challenging the validity of the '509 and '333 patents, and on August 23, 2019, challenging the validity of the '191 and '436 patents.[108]

C. CDC's Efforts to License Generic Products in United States

244. Because of the Gilead-owned patents related to Truvada® and the compounds contained therein, there is currently no generic equivalent to the Truvada® product in the United States.

245. Nonetheless, the Government's efforts to license the Patents-in-Suit and foreign counterparts are continuing for manufacturers seeking to sell generic Truvada® products in the United States.

246. As a result of its settlement with Gilead, Teva is expected to launch a generic Truvada® product in 2020 in the United States. FDA approved Teva's Abbreviated New Drug Application (ANDA) for its generic equivalent to Truvada® in June 2017. While Teva has

[107] *H. Comm. Hearing*, *supra* note 51, at 14.
[108] The PTO proceedings are: IPR2019-01453, IPR2019-0454, IPR2019-01455, IPR2019-01456.

communicated with NIAID/TTIPO, in 2017 and again in 2019, it has yet to take a license in the Patents-in-Suit.

247. Several other companies have also filed ANDAs seeking to market their own generic equivalent to Truvada® in the United States, including Aurobindo Pharma Ltd. (Aurobindo), Mylan, Cipla Ltd., Hetero Labs, Ltd., Pharmacare Ltd., and Strides Arcolab Ltd.

248. Although none is currently selling a generic equivalent to the Truvada® product in the United States, two of these companies (Mylan and Aurobindo) have received FDA approval of their ANDAs. Only Mylan has obtained a license to the Patents-in-Suit and has agreed to pay royalties for products sold or manufactured in the United States.

D. Gilead's Intellectual Property Relating to CDC's Inventive Regimens

249. While refusing to license or even acknowledge any Government intellectual property rights in PrEP, Gilead has, at the same time, pursued its own intellectual property protection in the PrEP market.

250. Gilead applied for and received a trademark in the United States for exclusive use of the mark, TRUVADA FOR PREP. Gilead's application for the mark was filed on January 6, 2017 with U.S. Ser. No. 87,292,084 and was registered on December 19, 2017 as U.S. Reg. No. 5,358,262.[109]

[109] TRUVADA FOR PREP, Registration No. 5,358,262, http://tsdr.uspto.gov/documentviewer?caseId=sn87292084&docId=ORC20171203050400#docIndex=0&page=1 [https://perma.cc/5GAS-MQGT] (Exhibit 79). Gilead has also received a registered trademark for Truvada for PrEP®'s logo. *See* EMTRICITABINE 200 MG / TENOFOVIR DISOPROXIL FUMARATE 300 MG TABLETS FOR PREP PRE-EXPOSURE PROPHYLAXIS, Registration No. 5,623,246, http://tsdr.uspto.gov/documentviewer?caseId=sn87227314&docId=ORC20181118032302#docIndex=0&page=1 [https://perma.cc/F7U7-JP5V] (Exhibit 80).

251. And in anticipation of Descovy®'s recent FDA approval for PrEP, Gilead has already sought similar protection for the mark, DESCOVY FOR PREP. Gilead's application was filed on January 17, 2019 as U.S. Ser. No. 88,266,226. [110]

252. All of Gilead's U.S. trademark applications were filed well after the Government provided Gilead with notice of the Patents-in-Suit and attempted to negotiate with Gilead for a license.

VII. GILEAD'S WILLFUL INFRINGEMENT OF CDC'S PATENTS

A. Inducement of PrEP Regimens Through Sales of Truvada®

253. Since 2012, when FDA approval was given for the use of Truvada® as PrEP, Gilead has marketed and sold Truvada® for that purpose.

254. Truvada® has been Gilead's top selling HIV medication, historically accounting for around 25 percent of its HIV product sales and almost 12 percent of its total product sales.

255. Since the '509 patent issued in mid-2015, Gilead has received approximately $6,709,000,000 in revenue from sales of Truvada® in the United States. While the percentage of Truvada® sales attributable to Truvada for PrEP® has fluctuated over time, Gilead reported in the first quarter of 2019 that more than 60 percent of those taking Truvada® were taking it for PrEP.

[110] U.S. Trademark Application Serial No. 88,266,226 (filed Jan. 17, 2019) [hereinafter Descovy Trademark Application], http://tsdr.uspto.gov/documentviewer?caseId=sn88266226&docId=RFA20190121141120#docIndex=9&page=1 [https://perma.cc/N2VS-TGN8] (Exhibit 81). Gilead has also applied for trademark registration of Descovy® for PrEP's logo. *See* U.S. Trademark Application Serial No. 88,615,918 (filed 09/13/2019), http://tsdr.uspto.gov/documentviewer?caseId=sn88615918&docId=RFA20190917080020#docIndex=1&page=1 [https://perma.cc/PG9W-TD97] (Exhibits 82).

256. In amassing these sales of Truvada for PrEP®, Gilead has repeatedly instructed health care providers and patients, in multiple ways, on administration of a Truvada for PrEP® regimen.

257. According to its FDA-mandated labeling, Truvada® contains FTC and TDF in several dosage combinations, including 200 mg FTC and 300 mg TDF.[111]

258. The labeling further states under "Indications and Usage" that Truvada® is indicated in combination "with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce risk of sexually acquired HIV-1 in adults at high risk." Under "Dosage and Administration," Gilead's FDA-approved prescribing information for pre-exposure prophylaxis states "[r]ecommended dose in HIV-1 uninfected adults: One tablet (containing 200mg/300 mg of emtricitabine and tenofovir disoproxil fumarate) once daily taken orally with or without food."[112]

259. Moreover, Gilead has actively promoted Truvada for PrEP®, and has for example made available a pamphlet entitled "TRUVADA for a Pre-Exposure Prophylaxis (PrEP) indication" to train healthcare providers in the selection and treatment of patients.[113]

260. Gilead also instructs the prescribing healthcare provider and the patient to sign a standard "Agreement Form" before initiating Truvada for PrEP®, and instructs prescribers to review the Agreement Form at each visit with the patient. The prescriber affirms in the Agreement that the HIV-negative status of the patient has been confirmed and that the prescriber has reviewed

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[111] TRUVADA [package insert]. Foster City, CA: Gilead Sciences, Inc. (revised May 2018), https://www.gilead.com/~/media/Files/pdfs/medicines/hiv/truvada/truvada_pi.pdf [https://perma.cc/YWA9-282K] (Exhibit 83).

[112] *Id.*

[113] Gilead Sciences, Inc., *TRUVADA for a Pre-exposure Prophylaxis (PrEP) Indication: Training Guide for Healthcare Providers*, THE AIDS INSTITUTE (2012), https://www.theaidsinstitute.org/sites/default/files/attachments/Training_Guide_for_Healthcare_Providers.pdf [https://perma.cc/3XW3-ESPS] (Exhibit 84).

the Truvada for PrEP® Medication Guide with the patient, and will continue to monitor the patient appropriately. The patient acknowledges being HIV-negative, agrees to repeat HIV testing every three months, and acknowledges having read the Truvada for PrEP Medication Guide.[114]

261. As further evidence of its intent that Truvada® be administered as a PrEP regimen, Gilead has obtained a trademark for Truvada for PrEP®.[115] Gilead has also applied for trademark protection of the phase "Step Up. PrEP Up." for use in promoting public awareness and providing medical information about the prevention HIV and AIDS.[116] Further, Gilead has applied to trademark blue, oblong tablets for "PrEP preparations for prevention and risk mitigation of contracting HIV."[117]

B. Gilead's Clinical Trials to Obtain FDA Approval of Descovy® for PrEP

262. On information and belief, Gilead, in recent years, has conducted and continues to conduct closely controlled clinical trials, including those needed to obtain FDA approval of Descovy® for PrEP.

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[114] *Agreement Form for Initiating Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg for HIV-1 Pre-exposure Prophylaxis (PrEP)*, GILEAD SCIENCES, INC. (May 2018), https://services.gileadhiv.com/content/pdf/truvadapreprems/2018-05-15-TVD-Prescriber%20Individual%20Agreement%20Form-Layout-SSS-PDF.pdf [https://perma.cc/8LXS-7PWV] (Exhibit 85).

[115] TRUVADA FOR PREP, *supra* note 109. As used herein, Truvada for PrEP® is used to generally describe the prescribed use of Truvada® as a PrEP regimen, regardless of whether the product labeling or packaging itself includes the Truvada for PrEP® mark.

[116] U.S. Trademark Application Serial No. 88,504,395 (filed July 8, 2019) [hereinafter Step Up. PrEP Up application], http://tsdr.uspto.gov/documentviewer?caseId=sn88504395&docId=FTK20190711083818#docIndex=7&page=1 [https://perma.cc/7AFM-X92K] (Exhibit 86).

[117] U.S. Trademark Application Serial No. 87,794,113 (filed Feb. 12, 2018), http://tsdr.uspto.gov/documentviewer?caseId=sn87794113&docId=RFA20180215074848#docIndex=23&page=1 [https://perma.cc/T2J3-4QQ6] (Exhibit 87) [hereinafter Blue, Oblong Tablet Application].

263. Such clinical trials include the DISCOVER trial,[118] titled "A Phase 3, Randomized, Double-blind Study to Evaluate the Safety and Efficacy of Emtricitabine and Tenofovir Alafenamide (F/TAF) Fixed-Dose Combination Once Daily for Pre-Exposure Prophylaxis in Men and Transgender Women Who Have Sex With Men and Are At Risk of HIV-1 Infection (DISCOVER)." Gilead was the sole sponsor of this trial, ostensibly designed to obtain FDA approval for Descovy® for PrEP. Gilead did not enlist any Government support or funding for the trial.

264. As designed by Gilead, the DISCOVER trial consisted of three experimental arms:

a) an experimental arm where the subject is given FTC/TAF (Descovy®, 200/25 mg tablet) for PrEP and an FTC/TDF placebo (Truvada for PrEP® placebo), each administered orally once daily;

b) an experimental arm where the subject is given FTC/TDF (Truvada for PrEP®, 200/300 mg tablet) and an FTC/TAF placebo (Descovy® placebo), each administered orally once daily;

c) an open-label extension experimental arm wherein, once all participants have been on blinded treatment for at least 96 weeks, the study will be unblinded and participants will be offered the option to continue on open-label FTC/TAF treatment for pre-exposure prophylaxis in the open-label extension for 48 weeks, where the open label FTC/TAF (Descovy®, 200/25 mg tablet) regimen is administered orally once daily.

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[118] Gilead Sciences, *Safety and Efficacy of Emtricitabine and Tenofovir Alafenamide (F/TAF) Fixed-Dose Combination Once Daily for Pre-Exposure Prophylaxis in Men and Transgender Women Who Have Sex with Men and Are at Risk of HIV-1 Infection (DISCOVER)*, CLINICALTRIALS.GOV (July 22, 2016) [hereinafter DISCOVER Trial], https://clinicaltrials.gov/ct2/show/NCT02842086 [https://perma.cc/4EUB-9P6D] (last updated Aug. 19, 2019) (Exhibit 88).

265. The DISCOVER trial tested "whether a combination of emtricitabine and tenofovir alafenamide (F[TC]/TAF) is as safe and effective as Truvada® (emtricitabine and tenofovir disoproxil fumarate, F[TC]/TDF) at reducing the risk of HIV infection when used as pre-exposure prophylaxis (PrEP)."[119] It enrolled more than 5,000 men and transgender women who were at risk of acquiring HIV in order to analyzethe efficacy and safety of Descovy® and Truvada® for PrEP in at-risk populations at 93 study locations in the United States.[120]

266. In March 2019, Gilead reported results from the trials and expressed its view that Descovy® performed as well as Truvada®. According to John McHutchison, AO, MD, Chief Scientific Officer and Head of Research and Development at Gilead, "[a]s the largest HIV prevention trial conducted to date, the DISCOVER trial results clearly demonstrate Descovy for PrEP™ achieved a clinical profile similar to the high efficacy of Truvada and a more favorable bone and renal safety profile."[121]

267. In April 2019, Gilead submitted a supplemental New Drug Application (sNDA) to FDA for once-daily Descovy® for PrEP based on the DISCOVER trial data. FDA approved the regimen on October 3, 2019.

268. Based on information and belief, the first two arms of the trial were completed by April 2019, when the data were reported, but the third arm (the open label extension of Descovy®

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[119] *Statement on DISCOVER Study of F/TAF for PrEP*, Gilead.com (Nov. 11, 2016), https://www.gilead.com/news-and-press/company-statements/discover-study-of-ftaf-for-*prep* [https://perma.cc/EPZ6-FLLX] (Exhibit 89).
[120] DISCOVER Trial, *supra* note 118.
[121] *Gilead Announces Data Demonstrating Non-Inferiority of Once-Daily Descovy® vs. Once-Daily Truvada® for Prevention of HIV Infection*, Gilead.com, (Mar. 6, 2019), https://www.gilead.com/news-and-press/press-room/press-releases/2019/3/gilead-announces-data-demonstrating-noninferiority-of-oncedaily-descovy-vs-oncedaily-truvada-for-prevention-of-hiv-infection [https://perma.cc/7TXX-C4H5] (Exhibit 90).

for PrEP) is continuing, and is expected to continue until September 2021, despite the recent FDA approval.

C. Inducement of PrEP Regimens Through Sales of Descovy®

269. Like Truvada®, Gilead is now marketing and selling Descovy® for PrEP after its recent FDA approval.

270. As Gilead holds U.S. patents related to its development of Descovy® as a treatment for HIV infections, it has not faced any generic competition in the United States.

271. Based on information and belief,Gilead is working to transition Truvada for PrEP® users to Descovy® for PrEP, in view of the generic Truvada® competition from Teva in 2020 and other generic manufacturers in the coming years.

272. Gilead has begun to instruct and will continue to instruct health care providers and patients, in multiple ways, on administration of a Descovy® for PrEP regimen.

273. According to its FDA-mandated labeling, Descovy® is now indicated for "pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex." Under "Dosage and Administration," the recommended dosage for Descovy® for PrEP is "one tablet (containing 200 mg of FTC and 25 mg of TAF) once daily taken orally . . . in HIV-1 uninfected adults and adolescents[.]"[122]

274. As further evidence of its intent that Descovy® be administered as a PrEP regimen, Gilead has sought a trademark for Descovy for PrEP,[123] and has begun encouraging healthcare

[122] DESCOVY [package insert]. Foster City, CA: Gilead Sciences, Inc. (revised October 2019), https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/208215s012lbl.pdf [https://perma.cc/K8ZQ-68RF] (revised Oct. 2019) (Exhibit 91).
[123] Descovy Trademark Application, *supra* note 110.

providers to "update [the] PrEP" of their patients "with Descovy®", including those currently prescribed Truvada for PrEP®.[124]

D. Willfulness and Deliberateness of Gilead's Activities

275. As discussed, Gilead's awareness of the Patents-in-Suit (and related patent applications) arose as early as 2008, when it reviewed scientific publications discussing the filing of a patent application relating to the use of Truvada for PrEP®. Moreover, Gilead recognized its induced infringement at least by 2015, at the time the '509 patent issued, when it was repeatedly invited to discuss licensing rights to the Patents-in-Suit.

276. Gilead has not contended, including in testimony before Congress, that its marketing and selling of Truvada for PrEP® and Descovy® for PrEP do not infringe the Patents-in-Suit.

277. Gilead has only asserted that the Patents-in-Suit are not valid in repeated public statements.

278. In making these statements, Gilead has failed to address the fact that CDC is widely acknowledged as being the first to demonstrate that FTC/tenofovir prodrug regimens are highly effective in preventing HIV infections and resulted in immediate changes to large human trials related to Truvada for PrEP®. These trials directly led to FDA approval of that regimen. Gilead's validity assertions likewise ignore the wide acclaim and recognition of the innovative and breakthrough CDC research leading to the Patents-in-Suit.

279. In accordance with the Government's infringement claims, Gilead has also provided Truvada® and Descovy® to health care providers and patients with instructions to use

[124] www.descovyhcp.com [https://perma.cc/3D3G-S5LZ] (Exhibit 92) (quoted language visible on archived link); *see also* Step Up. PrEP Up. Application and Blue, Oblong Tablet Application, *supra* notes 116, 117.

those products in an infringing manner while being on notice of or willfully blind to the Patents-in-Suit and its infringement thereof, since the '509 patent issued in 2015. In short, Gilead knew, or should have known, of the Patents-in-Suit and of its own infringing acts, or deliberately took steps to avoid learning those facts.

COUNT I:
GILEAD'S WILLFUL INFRINGEMENT OF THE '509 PATENT BASED ON TRUVADA FOR PREP® AND DESCOVY® FOR PREP

280. The Government realleges and incorporates by reference the allegations of paragraphs 1 to 279 of this Complaint.

281. The '509 patent issued on June 2, 2015. The Government has owned the '509 patent since it was issued.

282. The administration of Truvada for PrEP® according to the prescribing information infringes the '509 Patent. For example, the claims of the '509 Patent, including but not limited to Claims 1 and 13, are infringed by the administration of Truvada for PrEP® according to the prescribing information as shown in Exhibits 85, 86, and 87 attached hereto. Likewise, at least Claim 13 of the '509 patent is infringed by the administration of Descovy® for PrEP according to the prescribing information as shown in Exhibit 88 attached hereto.

283. On information and belief, Gilead induces infringement pursuant to 35 U.S.C. § 271(b) of at least Claims 1 and 13 of the '509 patent through its sales of Truvada for PrEP®. Gilead actively instructs doctors and patients to administer Truvada for PrEP®, including through clinical trials, prescribing information, product labels, and other product literature. Further, Gilead advertises and promotes Truvada® to the medical community and the general public for use in pre-exposure prophylaxis. When used as instructed, doctors prescribe and patients use Truvada for PrEP® to practice the patented method of the '509 patent.

284. On information and belief, Gilead also induces infringement pursuant to 35 U.S.C. § 271(b) of at least Claim 13 of the ’509 patent through its sales of Descovy® for PrEP. Gilead actively instructs doctors and patients to administer Descovy® for PrEP, including through its product labels. Further, Gilead advertises and promotes Descovy® to the medical community and the general public for use in pre-exposure prophylaxis. When used as instructed, doctors prescribe and patients use Descovy® for PrEP to practice the patented method of the ’509 patent.

285. On information and belief, Gilead specifically intends that its actions will result in infringement of at least Claims 1 and 13 of the ’509 patent, or subjectively believes that its actions will result in infringement of the ’509 patent, as set forth above. Gilead knew of the ’509 patent and knew or should have known that use of Truvada for PrEP® and Descovy® for PrEP according to the prescribing information infringes the ’509 patent no later than its issue date.

286. Gilead’s infringement of the ’509 patent has been and continues to be willful, rendering this case exceptional under 35 U.S.C. § 285. Specifically, on information and belief, when Gilead undertook the actions set forth above, there was a high likelihood that its actions constituted infringement and Gilead knew or should have known of the existence of this high likelihood. Gilead’s conduct was malicious, wanton, deliberate, consciously wrongful, flagrant, and in bad faith. This is especially true because, as set forth herein, the Government has attempted to negotiate in good faith an appropriate license.

287. Gilead’s actions in willfully infringing the Government’s patents are especially worthy of punishment and may properly serve as grounds for a finding of exceptionality under 35 U.S.C. § 285.

288. By its actions, Gilead has injured the Government and is liable to the Government for infringement of the ’509 patent pursuant to 35 U.S.C. § 271. The Government is entitled to

recover from Gilead all damages that the Government has sustained as a result of Gilead's infringement of the '509 patent, including without limitation no less than a reasonable royalty.

COUNT II:
GILEAD'S WILLFUL INFRINGEMENT OF THE '333 PATENT BASED ON TRUVADA FOR PREP®

289. The Government realleges and incorporates by reference the allegations of paragraphs 1 to 288 of this Complaint.

290. The '333 patent issued on June 2, 2015. The Government has owned the '333 patent since it was issued.

291. The administration of Truvada for PrEP® according to the prescribing information infringes the '333 Patent. For example, the claims of the '333 Patent, including but not limited to Claims 1 and 13, are infringed by the administration of Truvada for PrEP® according to the prescribing information as shown in Exhibits 85, 86, and 87 attached hereto.

292. On information and belief, Gilead induces infringement pursuant to 35 U.S.C. § 271(b) of at least Claims 1 and 13 of the '333 patent through its sales of Truvada for PrEP®. Gilead actively instructs doctors and patients on how to administer Truvada for PrEP®, including through clinical trials, prescribing information, product labels, advertising, and other product literature. Further, Gilead advertises and promotes Truvada® to the medical community and the general public for use in pre-exposure prophylaxis. When used as instructed, doctors prescribe and patients use Truvada for PrEP® to practice the patented method of the '333 patent.

293. On information and belief, Gilead specifically intends that its actions will result in infringement of at least Claims 1 and 13 of the '333 patent, or subjectively believes that its actions will result in infringement of the '333 patent, as set forth above. Gilead knew of the '333 patent and knew or should have known that use of Truvada for PrEP® according to the prescribing information infringes the '333 patent no later than its issue date.

294. Gilead's infringement of the '333 patent has been and continues to be willful, rendering this case exceptional under 35 U.S.C. § 285. Specifically, on information and belief, when Gilead undertook the actions set forth above, there was a high likelihood that its actions constituted infringement and Gilead knew or should have known of the existence of this high likelihood. Gilead's conduct was malicious, wanton, deliberate, consciously wrongful, flagrant, and in bad faith. This is especially true because, as set forth herein, the Government has attempted to negotiate in good faith an appropriate license.

295. Gilead's actions in willfully infringing the Government's patents are especially worthy of punishment and may properly serve as grounds for a finding of exceptionality under 35 U.S.C. § 285.

296. By its actions, Gilead has injured the Government and is liable to the Government for infringement of the '333 patent pursuant to 35 U.S.C. § 271. The Government is entitled to recover from Gilead all damages that the Government has sustained as a result of Gilead's infringement of the '333 patent, including without limitation no less than a reasonable royalty.

COUNT III:
GILEAD'S WILLFUL INFRINGEMENT OF THE '191 PATENT BASED ON TRUVADA FOR PREP®

297. The Government realleges and incorporates by reference the allegations of paragraphs 1 to 296 of this Complaint.

298. The '191 patent issued on June 2, 2015. The Government has owned the '191 patent since it was issued.

299. The use of Truvada for PrEP® according to the prescribing information infringes the '191 patent. For example, the claims of the '191 patent, including but not limited to Claims 1 and 13, are infringed by use of Truvada for PrEP® according to the prescribing information as shown in Exhibits 85, 86, and 87 attached hereto.

300. On information and belief, Gilead induces infringement pursuant to 35 U.S.C. § 271(b) of at least Claims 1 and 13 of the '191 patent through its sales of Truvada for PrEP®. Gilead actively instructs doctors and patients on how to administer Truvada for PrEP®, including through clinical trials, prescribing information, product labels, advertising, and other product literature. Further, Gilead advertises and promotes Truvada® to the medical community and the general public for use in pre-exposure prophylaxis. When used as instructed, doctors prescribe and patients use Truvada for PrEP® to practice the patented method of the '191 patent.

301. On information and belief, Gilead specifically intends that its actions will result in infringement of at least Claims 1 and 13 of the '191 patent, or subjectively believes that its actions will result in infringement of the '191 patent, as set forth above. Gilead knew of the '191 patent and knew or should have known that use of Truvada for PrEP® according to the prescribing information infringes the '191 patent no later than its issue date.

302. Gilead's infringement of the '191 patent has been and continues to be willful, rendering this case exceptional under 35 U.S.C. § 285. Specifically, on information and belief, when Gilead undertook the actions set forth above, there was a high likelihood that its actions constituted infringement and Gilead knew or should have known of the existence of this high likelihood. Gilead's conduct was malicious, wanton, deliberate, consciously wrongful, flagrant, and in bad faith. This is especially true because, as set forth herein, the Government has attempted to negotiate in good faith an appropriate license.

303. Gilead's actions in willfully infringing the Government's patents are especially worthy of punishment and may properly serve as grounds for a finding of exceptionality under 35 U.S.C. § 285.

304. By its actions, Gilead has injured the Government and is liable to the Government for infringement of the ’191 patent pursuant to 35 U.S.C. § 271. The Government is entitled to recover from Gilead all damages that the Government has sustained as a result of Gilead’s infringement of the ’191 patent, including without limitation no less than a reasonable royalty.

COUNT IV:
GILEAD’S WILLFUL INFRINGEMENT OF THE ’423 PATENT BASED ON TRUVADA FOR PREP® AND DESCOVY® FOR PREP

305. The Government realleges and incorporates by reference the allegations of paragraphs 1 to 304 of this Complaint.

306. The ’423 patent issued on June 2, 2015. The Government has owned the ’423 patent since it was issued.

307. The use of Truvada for PrEP® and Descovy® for PrEP according to the prescribing information for each infringes the ’423 Patent. For example, the claims of the ’423 Patent, including but not limited to Claims 1 and 12, are infringed by administration of Truvada for PrEP® according to the prescribing information as shown in Exhibits 85, 86, and 87 attached hereto. Likewise, at least Claim 12 of the ’423 patent is infringed by the administration of Descovy® for PrEP as shown in Exhibit 88 attached hereto.

308. On information and belief, Gilead induces infringement pursuant to 35 U.S.C. § 271(b) of at least Claims 1 and 12 of the ’423 Patent through its sales of Truvada for PrEP®. Gilead actively instructs doctors and patients on how to administer Truvada for PrEP®, including through clinical trials, prescribing information, product labels, advertising, and other product literature. Further, Gilead advertises and promotes Truvada® to the medical community and the general public for use in pre-exposure prophylaxis. When used as instructed, doctors prescribe and patients use Truvada for PrEP® to practice the patented method of the ’423 patent.

309. On information and belief, Gilead also induces infringement pursuant to 35 U.S.C. § 271(b) of at least Claims 1 and 12 of the ’423 patent through its sales of Descovy® for PrEP. Gilead actively instructs doctors and patients to administer Descovy® for PrEP, including through clinical trials and its product labels. Further, Gilead advertises and promotes Descovy® to the medical community and the general public for use in pre-exposure prophylaxis. When used as instructed, doctors prescribe and patients use Descovy® for PrEP to practice the patented method of the ’423 patent.

310. On information and belief, Gilead specifically intends that its actions will result in infringement of at least Claims 1 and 12 of the ’423 patent, or subjectively believes that its actions will result in infringement of the ’423 patent, as set forth above. Gilead knew of the ’423 patent and knew or should have known that use of Truvada for PrEP® and Descovy® for PrEP according to the prescribing information infringes the ’423 patent no later than its issue date.

311. Gilead’s infringement of the ’423 patent has been and continues to be willful, and Gilead’s conduct renders this case exceptional under 35 U.S.C. § 285. Specifically, on information and belief, when Gilead undertook the actions set forth above, there was a high likelihood that its actions constituted infringement and Gilead knew or should have known of the existence of this high likelihood. Gilead’s conduct was malicious, wanton, deliberate, consciously wrongful, flagrant, and in bad faith. This is especially true because, as set forth herein, the Government has attempted to negotiate in good faith an appropriate license.

312. Gilead’s actions in willfully infringing the Government’s patents are especially worthy of punishment and may properly serve as grounds for a finding of exceptionality under 35 U.S.C. § 285.

313. By its actions, Gilead has injured the Government and is liable to the Government for infringement of the ’423 patent pursuant to 35 U.S.C. § 271. The Government is entitled to recover from Gilead all damages that the Government has sustained as a result of Gilead’s infringement of the ’423 patent, including without limitation no less than a reasonable royalty.

PRAYER FOR RELIEF

WHEREFORE, the United States prays for a judgment in its favor and against Gilead and respectfully requests the following relief:

A. A judgment declaring that Gilead has infringed, either literally or under the doctrine of equivalents, one or more claims of the Patents-in-Suit.

B. A finding that Gilead’s infringement of one or more claims of the Patents-in-Suit has been willful and a judgment for enhanced damages;

C. A judgment awarding the Government damages adequate to compensate for Gilead’s infringement;

D. Pre-judgment and post-judgment interest to the full extent allowed under the law, as well as its costs;

E. An ongoing royalty for continued infringement pursuant to 35 U.S.C. § 283;

F. Attorneys’ fees in this action as an exceptional case pursuant to 35 U.S.C. § 285;

G. Costs and expenses in this action; and

H. Such other and further relief as the Court deems just and proper.

Respectfully submitted,

Dated: November 6, 2019

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